

Jury to hear racas case

up going on. I can say that emphatically."

One of those injured, Vincent J. Bordonaro, 54, is in critical condition at Massachusetts General Hospital with severe head wounds. Sources close to the investigation said Bordonaro is near death.

Most of the other injured men were in Balliro's Boston offices yesterday for a press conference that Balliro said he called to put pressure on lawmen to investigate the attack.

The people who were at the Chelsea motel claim that John McLeod, an Everett policeman, organized the attack on them. McLeod was released from Whidden Memorial Hospital in Everett. CHELSEA, Page 13

meter workers ed under probe

James Campbell of Roslindale, who left his job as a meter-revenue collector five weeks before all the other members of the collection crew were arrested and charged with skimming from the city's meters at a rate of \$500,000 to \$700,000 a year, the sources said. Campbell's mother is Evelyn Campbell, Mayor Kevin H. White's Roslindale ward boss.

The sources said interest in Campbell has grown in the weeks since his former coworkers were arrested on larceny charges because investigators reportedly have learned that Campbell was making almost weekly deposits of \$300 to \$500 - including large amounts of quarters and dimes - in a Roslindale.

METERS, Page 13

New illness spreading, officials say

By Loretta McLaughlin
Globe Staff

A mysterious new disorder, originally afflicting only homosexual men but now occurring in certain groups of heterosexual men and women, is fast becoming a health problem that may soon explode into epidemics, according to recent reports.

Most worrisome are indications that the syndrome, which includes rare forms of cancer, pneumonia and infections, may be transmissible through transfusions of blood or blood byproducts.

A special conference will be held today by the US Department of Health and Human Services to review what is currently known that seems to link the deadly disorder to transfusions of blood components and what, if anything, can be done about this potentially major health hazard.

It was first suspected that the disorder might be passed through blood transfusions when, over the past four months, three cases of the

BLOOD, Page 4

Three banks reduce prime lending rate

Three major banks yesterday cut their prime lending rate a half point to 15½. Manufacturers Hanover Trust Co. of New York made the move after Wachovia Bank & Trust Co. of Winston-Salem, N.C., cut its rate to 15½ percent. Chemical Bank of New York also adopted the lower rate. Page 48.

Israel's right and 338, which have provided the framework for efforts to resolve the Arab-Israeli conflict.

"We have indicated this must be done in a clear and unequivocal way," said Larry Speakes, deputy White House press secretary, and Dean Fischer, the State Department spokesman. "The statement by Arafat does not meet our conditions," they said.

ARAFAT, Page 12

Israel blasts arms depot; Sudan offers to take PLO

From Wire Services

BEIRUT - Israeli jets scored a direct hit on a huge Palestinian ammunition dump yesterday, setting off a chain reaction of explosions that rocked the Lebanese capital for over an hour and sent plumes of smoke over the city.

It was the fifth straight day that Israeli air power battered Palestinian guerrillas in West Beirut, and came as Sudan reportedly offered to accept the PLO guerrillas.

The official government news agency quoted President Gaafar Nimeiri as saying, "Sudan is ready to receive the Palestinian fighters in Lebanon who were exposed to the conspiracies of many parties."

The agency said Nimeiri also offered to allow the PLO to use its office in the Sudanese capital.

MIDEAST, Page 12

Health costs m

By Thomas Oliphant
Globe Staff

WASHINGTON - The cost of health care in the United States is ballooning out of control, rising at roughly twice the general rate of inflation, eating into income and running at more than \$1200 for each man, woman and child in the country.

The government reported yesterday that health care spending shot up by 15.1 percent last year, reaching a total of nearly \$287 billion not counting research and construction expenditures, and accounting for 9.8 percent of the economy's total output of goods and services - the highest share ever.

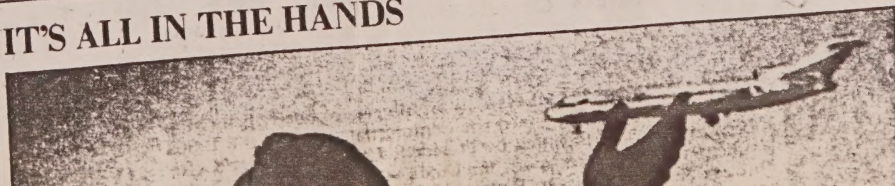
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IT'S ALL IN THE HANDS



HCHS

VOL. 1, NO. 2

SUMMER, 1979

newsletter

HCHS PLANS EXPANSION OF COMPREHENSIVE SERVICE TO GAYS ●

Staff and Board of the Homophile Community Health Service have begun work on a plan which will result in a more comprehensive service program for the gay community. The first phase of the plan entails internal restructuring within HCHS. Leadership of the agency's three components (the Clinic; the Alcoholism Treatment Service; the Hotline) and the agency's support services administrator are meeting weekly with Executive Director Susan Rosen to increase communication and coordination among the components, and to assess the community's needs for expansion of current services and development of new programs. New funding services are being sought both on state and Federal levels. In addition to increased communication and a needs assessment, priority is being given to raising the support service capacity of the agency, something which would be a necessary antecedent to a further expansion of services.

In performing a needs assessment, contact has been made with other gay and lesbian medical and mental health providers. Under consideration is a possible coalition of provider groups which would jointly develop a comprehensive community mental health, medical and alcoholism treatment service for gay people in Eastern Massachusetts.

Increasing the political visibility of gay and lesbian service providers is another agenda item on the HCHS plan. It was for this reason that agency staffers Susan Rosen and Joel Hencken have taken the lead in developing the new National Association of Gay Service Centers, an organization which will provide coordination to the efforts of gay service centers nationally and a political base for lobbying for funds on the Federal level.

A similar effort to establish a political base for gay alcoholism services providers will be made by HATS Director Robert Connolly at the August, 1979 national meeting of the National Association of Alcoholism Providers.

On a state level, the visibility of HCHS in the political process has been increased over the past year through the participation of the agency in several key advocacy and provider groups. HCHS is a member of the Coalition for Mental Health and Mental Retardation, the state's most powerful advocacy group in these fields; the Massachusetts Association for Mental Health; the Massachusetts Coalition of Human Service Providers; the Massachusetts Association of Alcoholism Providers; the Massachusetts Council on Alcoholism; and the Boston Council on Alcoholism. Participation in these advocacy groups is helpful to HCHS as a way of increasing agency visibility and as a way of presenting the needs of the gay community to the widest audience of decisionmakers in the mental health and alcoholism treatment fields.

States Executive Director Rosen, "We strongly feel that needs are not being met for specialized services to hundreds of thousands of gay people in the state. It is time for the gay community itself to start to plan to provide a comprehensive service to meet these needs over the next decade after Stonewall."

Community members who are interested in participating in the planning process for expansion of services are invited to join the HCHS Advisory Planning Council. To indicate interest, please call the agency at 542-5188.

FISCAL YEAR '80 FUNDING LOOKS SAFE FOR HCHS CLINICAL PROGRAM ●

AN UPDATE FROM SUSAN ROSEN. . . .

The purchase-of-service contract between HCHS and the Massachusetts Department of Mental Health, begun last September and due to expire on June 30th, will be continued with a small increase if the Department of Mental Health (DMH) fiscal year '80 budget request

is approved in the Massachusetts legislature. State Representative Barney Frank informed the Health Service that \$42,400 had been set aside for the clinic in the DMH FY '80 budget. The sum represents a continuation of the current funding level, plus a 6% cost of living increase which is being awarded to most DMH-funded programs. The contract would continue to fund the services of three HCHS clinical staff members as well as providing monies for professional consultation, and space rental.

"We are glad that DMH Commissioner Okin and EOHS Secretary Mahoney have shown their confidence in the work our clinic is doing to meet the mental health needs of gay people," said Susan Rosen recently.

GAYS ORGANIZE FOR NATIONAL ACTION ON HEALTH ISSUES ●

Three major resolutions affecting national politics and a new national organization emerged from the second annual National Gay Health Conference which met May 18-20 at Hunter College in New York City, with Joel Hencken, HCHS Clinical Director, and eight other HCHS staff attending. Attended by over 1,000 professionals in medicine, mental health, and alcoholism treatment, the conference was sponsored by the National Gay Health Coalition, an organization consisting of representatives from the lesbian and gay caucuses of professional organizations in the human services.

Resolutions which passed the convention include a resolution urging that gays be recognized as a special needs minority for all mental health services provided under Federal legislation now being written to revise the Community Mental Health Act. A resolution also passed in support of the proposed National March on Washington for Lesbian and Gay People, scheduled for October 14, 1979. Also passed was a resolution demanding input by gay representatives on the 1981 White House Conference on the Family.

Further actions of the conference included organization of a Task Force on Federal Health Legislation to organize input into new health-related legislation, such as the National Health Insurance plan; and the establishment of a non-profit foundation, The National Education Foundation for Gay Health, which will sponsor further meetings and publish a professional journal, the Journal of Gay Health Issues.

AT THE CONFERENCE. . . ●

HCHS LEADS THE WAY as Clinical Director, Joel Hencken authored the three resolutions on Federal legislation, the White House Conference on the Family and the March on Washington. He then went on during the brief three-day meeting period working with the organizing committee of the new National Association of Gay Service Centers (an outgrowth of the Conference) and became chairperson of the Task Force on Federal Health Legislation. Also present was Ron Vachon, of the Gay Health Collective at the Fenway Community Health Center. Mr. Vachon was Northeast Coordinator for the National Gay Health Conference. Congratulations to Joel Hencken on his new position.

THE NEW NATIONAL ORGANIZATION which was formed is the National Association of Gay Service Centers, and organization of human service providers in gay communities across the country. HCHS Executive Director, Susan Rosen, will be co-chair. The new organization has already scheduled regional meetings for November 1979, and a national meeting on the West Coast for November of 1980. The Northeast Regional meeting is likely to be held in Boston.

CLINIC UPDATE ●

CLINICAL DIRECTOR APPOINTED / HCHS PROGRAM PRAISED. . .

Staff Notes: In mid-January of this year, Joel Hencken, M.A., joined the HCHS staff as the agency's first Clinical Director. Joel will be providing leadership in case management, staff supervision, community liaison, inservice education, and program planning. Joel studied medicine at the University of California at San Diego and clinical psychology at San Diego State University before returning to his home state of Michigan to pursue a Ph.D. in clinical psychology at the University of Michigan. He received his M.A. in 1976 and expects completion of his doctorate in 1981.

Joel Hencken has taught psychology at SDSU and at the University of Michigan, and has done clinical work in a variety of college, hospital and community mental health settings. He is a member of the Steering Committee of the Association of Gay Psychologists, Associate

Editor of the Journal of Homosexuality, and a consultant on two research projects currently under consideration for NIMH funding. His current research is on gay identity formation.

Clinical Program Evaluated by DMH: On April 10, the DMH Region IV Quality Assurance Team visited HCHS to evaluate the clinical program. The evaluation was done pursuant to the purchase-of-service contract between HCHS and the Department of Mental Health. Administrative and clinical staff spent 5 hours with the evaluators, who looked at the clinic's physical setting, outreach, client services, involvement of clients in treatment planning, continuity of care, and community orientation. The clinic was evaluated on a 4-point scale from "not in compliance," to "full compliance." In no area did the clinic fall below "substantial compliance." The evaluators rated the clinic on a 4-point scale: ratings of 3.5 and 4 were given for client rights, continuity of care, community orientation, physical setting, outreach and staffing.

HCHS HELPS IN FORMATION OF "PARENTS AND FAMILIES OF GAYS" ●

The first active Massachusetts "Parents and Families of Gays" (PAFG) group was organized this past summer with the help of two HCHS staff members. In the ten months of its existence, Jean Riseman and Ron Wozniak have been involved as resource people and as a contact between prospective members and the group. Ron and Jean have also recruited and coordinated the involvement of resource people from other gay community organizations, including Dignity, Integrity, Clearspace and the Gay Hotline.

More than 50 parents, brothers and sisters of gay men and lesbians have been involved in the Boston PAFG group. The organization provides the only opportunity in Massachusetts for family members to share feelings and concerns, to provide support to each other and, indirectly, to support their gay relatives. The availability of PAFG helps families deal with the lack of public information about gay issues and the isolation that everyone involved feels at first.

In its short history, the group has already accomplished a great deal. Individuals have helped each other and formed ties of respect and friendship. As a group, people are actively defining the purpose and direction of PAFG, deciding on ways to reach out to others, and considering relations with the gay community as a whole. Some of the questions which are currently being dealt with include: how to handle the tremendous geographic spread of the members; how quickly to expand membership; and what types of meetings best suit differing needs. At present, one public meeting has been held at the Episcopal Divinity School, and another is being planned. Other meetings are more informal and are held in people's homes.

The birth of PAFG aroused interest in the formation of a similar group for young adults with a gay parent. This group, which is just in the formative stage, is modeled after PAFG and is benefiting greatly from the older group's experience. HCHS staff are also involved in referring potential members and as resource people.

HOTLINE UPDATE. . . ●

Over the past six months, the Hotline has seen impressive growth in its services, staff, and training program. In May, 875 calls were received by Hotline listeners, a 100% increase over the number of calls received on a monthly basis in 1978. The telephone listening staff of the Hotline is now up to 37, an increase from 21 since December, 1978. The expansion of the Hotline staff has made it possible to reopen the 3-6 p.m. shift, so that the Hotline is now taking calls from 3 p.m. - midnight, Monday through Friday.

In addition to the general growth of staff, several special objectives of the Hotline are being attained in staffing. The number of women who serve on the Hotline has grown over the past six months from two to nine. Longevity of service on the Hotline has also increased. At the end of May, there were 13 staffers who had served on the Hotline for 12 months or more. This is unusual for a volunteer telephone counseling service, where turnover is usually very high. Expansion of the training program may be helping to hold qualified staff. Recently, the Hotline training package has been revamped, so that it now consists of 35 hours of on-line and workshop training, over a period of ten weeks, followed by regular inservice education sessions.

The Gay Hotline participates in several statewide organizations which bring together other telephone listening services. These groups include the Massachusetts Crisis Intervention Association, and the Massachusetts Information and Referral Coalition, which is sponsored by the United Way of Massachusetts. In addition to membership in these organizations, the Hotline has reached out to other listening services, training their staffs on gay and lesbian issues.

UPDATE ON H.A.T.S. . . . ●

HATS staff has been very busy during the past couple of months: in January, we learned from the Division of Alcoholism that funding would be terminated at the end of this fiscal year. Well, here we are, and after a long struggle through our work with the Special Populations Subcommittee of the Governor's Advisory Council on Alcoholism, the Chairperson of the Council made a strong recommendation for continued funding. We have received "official" notification that funding will continue with a 25% increase for the next two years--\$18,592 for fiscal year 1980 and \$19,894 for fiscal year 1981.

Media exposure and an increase in public appearance of support both by HATS staff and others have aided us in securing this continued funding. The work that went on to insure a favorable outcome included attention to a Boston Globe article on Gay Alcoholism in February; an appearance before the Regional Hearing to testify for the need for Alcoholism Services for the Gay Community in early March; and in April, appearances on the Don Latulip Talk Show (WROR-FM) and WBUR's GayWay program to air the issue of alcoholism in the Gay Community.

NEW DIRECTIONS FOR H.A.T.S. . . . ●

The HATS Advisory Council which was formed in February to assist and advise the Gay Community in the development of alcoholism services is comprised of a variety of community members and chaired by Mr. Rich Morgan. A new sub-committee developed from the Advisory Council is the Gay and Lesbian Half Way House Committee. This sub-committee has incorporated and applied for tax exempt status through the assistant of Attorney John Ward. The work of this sub-committee will be to advocate for the first co-ed residential treatment facility for Gay recovering alcoholics--a priority need for our community. The second priority for the Advisory Council will be to set up a state-wide Council on Gay alcoholism, encouraging input and advocacy for statewide gay services.

We have joined with the Mayor's Council on Substance Abuse as a participating member. . . Outreach efforts continue through inservice education. We have recently received some invitations to address staffs in out-lying and suburban facilities. . . Delivery of services continues to grow and expand, new groups have been formed. . . The client load has tripled within the past nine months!

We are still interested in community input, both the Advisory Council and the Half Way House Sub-committee welcome new members. Anyone interested in offering service or financial contribution is urged to contact Robert Connolly, Project Director at 426-5208.

OTHER NOTES ● ROBERT CONNOLLY. . . ●

Mayor Kevin H. White appointed Robert Connolly of Jamaica Plain as a member of the Coordinating Council on Drug Abuse. The Council, which was established by ordinance in 1969, is charged with the responsibility for coordinating the work of public and private agencies dealing with substance abuse. The Council is also responsible for developing substance abuse education programs and for advising the Mayor on drug policy.

"An experienced alcohol rehabilitation counselor and program administrator, Connolly has been the project director of the Homophile Alcohol Treatment Service since 1978," reads a news release from the Mayor's office on May 8 of this year. Congratulations to Robert Connolly.

SUSAN ROSEN. . . ●

Executive Director Susan Rosen was invited to give a paper at the American College Health Association National Conference in Washington at the end of May. The paper was on "Meeting the Mental Health Needs of Lesbian and Gay College Students."

While in Washington, Susan visited the Federal Relations Office of the City of Boston, and met with staff from the office of Rep. Gerry Studds (Southeastern Massachusetts), Rep. James Shannon (Lawrence-Lowell area) and Senator Paul Tsongas. The Boston lobbyists and Massachusetts representatives were very helpful, reports Susan, in listening and actively giving ideas for better and more substantial funding for the Health Service. It was the first time that HCHS has been in Washington actively seeking support.

One of the major issues facing the agency and other mental health facilities across the country is a pending revision of the Community Mental Health Act which established Federal funding for community mental health programs along geographic lines - a model which over the years has proved ineffective for minorities. The new Community Mental Health Systems Act recommends funding "core service agencies" specifically to serve "priority populations," which the act defines as children, the elderly, racial and ethnic groups and "others." The issue is whether gays will be included among the "others," something that was probably not originally intended. Susan talked to staff of Rep. Barbara Mikulski who is on the House subcommittee where the bill is now being considered, and with Steve Endean of the National Gay Rights lobby, relative to the bill and the problems HCHS will have with Federal funding if the new law is interpreted as being limited in scope.

! IN THE NEWS. . .

TIME MAGAZINE, April 23, 1979 carried a major article on gay life in America in which appeared, "In Boston, the Homophile Community Health Service provides psychological counseling for gays who fear that straight doctors will tell them that the source of all gays' problems is their homosexuality." (It was a generally positive article, more news oriented than opinionated. ed.)

THE BOSTON GLOBE, February 18, 1979, had an article, "Gay Boston is a Reality," which described HCHS as the "key provider (of mental health services for gay people) in the Boston area. It is a fully licensed non-profit clinic that has dealt with more than 3,000 patients over the years, including parents and children of gays." A feature story, the Globe article was primarily reporting on successes and problems of gays in Metropolitan Boston. In the article, Executive Director Susan Rosen called attention to the fact that so often a gay person's problems are no more serious than those of a straight person; but because gays cannot openly discuss these problems as heterosexuals do, depression and anxiety may become greater for the gay person who lacks support.

There are many ways that you can help with the growth of HCHS. Donations, both large and small, are always needed to help expand our services and facilities.

Gifts of office equipment and furniture such as file cabinets, chairs, typewriters, adding machines and miscellaneous accessories in good condition are very much in need during our current expansion. Persons interested in volunteering time, both professionally or to assist in other areas, should contact us to discuss time allotments.

All contributions of a financial or material nature are tax deductible.

☐ YES, I would like to give my support to HCHS. Enclosed is my contribution \$ _____.

☐ I am interested in volunteering time for HCHS.

Please call me at _____ between the hours of _____ to _____.

Name _____

Address _____

City _____ State _____ Zip _____.

Checks or money orders may be made payable to Homophile Community Health Service or to Counseling Services, Inc.





PHONE (617) 542-5188
542-6075

HOMOPHILE COMMUNITY HEALTH SERVICE • 80 BOYLSTON ST., S.855, BOSTON, MASS. 02116
AFFILIATED WITH BOSTON UNIVERSITY MENTAL HEALTH TREATMENT, TRAINING AND RESEARCH CENTER

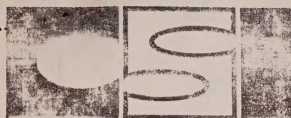
Richard C. Pillard, M.D.
Medical Director

We at the Homophile Community Health Service, a non-profit mental health center for the gay community, are updating our referrals. We hope to obtain as wide a network of referrals as possible from throughout the New England area— therapists who service women and/or men, and who are supportive of lesbian and gay male lifestyles. We are interested in the community which you service, the kinds of therapy offered (individual, couple, group), as well as your overall style (gestalt approach, Rogerian, bioenergetics, etc.). In the process of updating our referrals, we would appreciate your sharing as much information about your work as seems appropriate. On the following page is a list of the areas we feel would be most helpful to know of in referring a client to your services. Enclosed is a stamped, self-addressed envelope from the clinic.

Thank you for your time and help.

Sincerely,

James Fishman



PHONE (617) 542-5188
542-6075

COUNSELING SERVICE INC. • 80 BOYLSTON ST., S.855, BOSTON, MASS. 02116

AFFILIATED WITH BOSTON UNIVERSITY MENTAL HEALTH TREATMENT, TRAINING AND RESEARCH CENTER

(COUNSELING SERVICE+ INC. does business as: THE HOMOPHILE COMMUNITY HEALTH SERVICE)

GENERAL INFORMATION

THE HOMOPHILE COMMUNITY HEALTH SERVICE is a mental health clinic serving primarily the homophile community of metropolitan Boston and outlying areas of New England. HCCHS has been in operation since January 1971. During this time we have seen over 5000 clients, of whom 450 are now being counseled with 110 undergoing regular weekly therapy. Thirty new clients are being seen every month. About sixty-five percent of our clients are male, we are doing affirmative action for both women and non-whites.

Our services include general counseling, telephone (hot-line) counseling, individual and group therapy, crisis intervention, social work, education, and special events. Our clinical staff of thirty-five includes psychiatrists, clinical psychologists, psychiatric nurses, social workers, pastoral counselors, and paraprofessional therapists. HCCHS is incorporated as a not-for-profit corporation by the Commonwealth of Massachusetts. ALL CONTRIBUTIONS ARE TAX DEDUCTIBLE.

The service emphasizes empathetic counseling for same-gender oriented persons. In line with the American Psychiatric Association's definition, homosexuality per se is not considered a sickness, though conflict with sexual orientation may be a factor with some clients. Our therapists treat neither homosexuality nor heterosexuality, they think of individuals and their particular needs. Clinical services also include two special programs: a Family Services Program, assisting those close to or related to same-gender oriented persons, and an Alcohol Services Program which is concerned both with counseling and liaison work with other alcohol facilities in the area. Our clinical experience indicates a large number of clients are troubled by the past and present attitudes of society toward same-gender oriented persons. Clients whose lives are troubled by many and varied circumstances are helped to put together for themselves better integrated and more satisfying lives. In these regards, HCCHS attempts to help both its clients and society at large toward a better understanding of homosexuality.

HCCHS is affiliated with Boston University Mental Health Treatment, Training, and Research Center. We are licensed as a mental health agency by the Department of Public Health. We have acted as consultant for the establishment and operation of several similar homophile health services around the country. Offering a rare opportunity to work with a minority group in a therapeutic atmosphere, the Service is an accredited field work placement center for Boston University's Graduate Schools of Nursing and Social Work; for the Boston Theological Institute (a consortium of Boston area Divinity Schools); Northeastern University's Department of Education Counselors, Goddard's Graduate School of Social Change, and others.

We maintain an active out-reach education program, including clinical conferences, speaking engagements on a variety of homophile and homophile related topics, and staff training for other social service and community agencies. As part of this program, the Institute for Homophile Studies is affiliated with several college-level courses on homosexuality in literature, history, and contemporary society. HCCHS maintains an extensive resource library on homosexuality which is made available to students and the community at large.

In addition, HCCHS sponsors a number of special events each year. In the past, these have included such diverse offerings as: an opera, a women's film festival, folk concerts, and public lectures. HCCHS sponsors and produces GAY WAY, on WBUR-FM 90.9 radio as well

A NON PROFIT CORPORATION — ALL CONTRIBUTIONS TAX DEDUCTIBLE

The New England Journal of Medicine

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Volume 296.

APRIL 21, 1977

Number 16

SPECTINOMYCIN VERSUS TETRACYCLINE FOR THE TREATMENT OF GONORRHEA

WALTER W. KARNEY, M.D., ALF H.B. PEDERSEN, M.D., M.P.H., MORTON NELSON, M.D., M.P.H.,
HARRY ADAMS, M.D., ROBERT T. PFEIFER, M.D., AND KING K. HOLMES, M.D., PH.D.

Abstract Spectinomycin and tetracycline are alternative drugs to penicillin in the treatment of gonorrhea. To compare the efficacy of these agents and their propensity to select resistant gonococci, we treated 4043 patients randomly with either 2 or 4 g of spectinomycin once or 9 g of oral tetracycline for four days. Minimum cure rate for anogenital gonorrhea was 94 per cent with either drug. Oropharyngeal infection responded poorly to spectinomycin in men, with failure of therapy in six of 11. Postgonococcal urethritis in men was less common after tetracycline

than after spectinomycin ($P < 0.005$). Spectinomycin failure was not related to drug resistance. Tetracycline failure correlated with resistance ($P < 0.0002$); one fifth of the isolates resistant to 1.0 μg per milliliter of tetracycline were not eradicated. For several reasons, including the appearance of β -lactamase-producing gonococci, it is no longer clear that penicillin G is the "drug of choice" for gonorrhea. Spectinomycin and tetracycline are equally acceptable alternatives, each with distinct advantages and disadvantages. (N Engl J Med 296:889-894, 1977)

TETRACYCLINE hydrochloride and spectinomycin hydrochloride are the two non-penicillin antibiotics most commonly advocated in the United States for the treatment of gonorrhea, but it has been recommended that they be used as initial therapy only for patients with penicillin allergy.¹ Spectinomycin is also recommended as the antibiotic of choice for patients with gonorrhea who are not cured by other antimicrobials.¹ One reason for reserving tetracycline for patients with penicillin allergy is that single-dose tetracycline therapy is not at all effective for gonorrhea and leads to selection of relatively resistant gonococci, with minimal inhibitory concentrations of tetracycline in vitro in the range of 1 to 4 μg per milliliter.² Compliance with multiple-dose tetracycline therapy is therefore required. Experience with the currently recommended four-day tetracycline regimen¹ has been relatively limited in the United States,³ and it has not yet been determined how effective the four-day regimen would be against relatively resistant strains. Since the daily dose of tetracycline cannot be further increased without toxicity, there is concern that if re-

sistance at the level of 1 to 4 μg per milliliter does cause appreciable failure rates with the four-day regimen, increasing use of tetracycline for gonorrhea could eventually lead to selection of gonococci that could no longer be treated effectively by tetracycline therapy.

Two strains of *Neisseria gonorrhoeae* that are totally resistant to spectinomycin have been encountered in Denmark,⁴ and one has recently been isolated in Atlanta, Georgia (Brown ST: personal communication). Such isolates can also be selected in vitro.⁵ The principal reason for reserving spectinomycin for a backup treatment for gonorrhea has therefore been the justifiable fear of selection and emergence of such spectinomycin-resistant variants. The recent isolation of β -lactamase-producing strains of *N. gonorrhoeae* throughout the world⁶⁻⁹ raises a similar fear that such strains will be increasingly selected by continued use of penicillin or ampicillin therapy. A second reason why the penicillins can no longer be considered ideal therapy for gonorrhea is that *Chlamydia trachomatis*, which causes many cases of nongonococcal urethritis¹⁰⁻¹⁴ and postgonococcal urethritis,^{10,11,15,16} can be isolated from about 20 per cent to 30 per cent of men¹⁰⁻¹² and 30 per cent to 60 per cent of women¹⁷⁻¹⁹ with gonorrhea, and is not affected by penicillin or ampicillin therapy.¹⁶ Tetracycline is active against all strains of *C. trachomatis* and also against most strains of *Ureaplasma urealyticum*,²⁰ another penicillin-resistant bacterium recently implicated as a possible cause of chlamydia-negative nongonococcal urethritis.^{14,21}

From the departments of Medicine, University of Washington School of Medicine, and U.S. Public Health Service Hospital, Seattle, WA, the Seattle-King County and Alameda County Health Care Services Agency, Oakland, CA, and the Department of Family Medicine, University of California, College of Medicine, Irvine, CA (address reprint requests to Dr. Holmes at the Division of Infectious Diseases, U.S. Public Health Service Hospital, Seattle, WA 98114).

Supported by a research grant (CC 00593) from the Center for Disease Control, Atlanta, GA, a grant (AI 12192) from the National Institutes of Health and a grant from the Upjohn Company.

Spectinomycin has only marginal activity against *C. trachomatis*,^{22,23} but has definite activity against *U. urealyticum*.^{14,24} For these various reasons, it is anticipated that spectinomycin and tetracycline may be used increasingly for primary treatment of gonorrhea, even though spectinomycin is now more expensive than tetracycline or penicillin, and is not effective for concomitantly acquired incubating syphilis.

The present collaborative study was undertaken to determine whether extensive use of spectinomycin in two communities would lead to the appearance of spectinomycin-resistant strains of *N. gonorrhoeae*, and whether tetracycline treatment failure was related to resistance of gonococci to tetracycline, and to compare the efficacy of spectinomycin and tetracycline for the treatment of uncomplicated genital and anal gonococcal infection. The study was not designed to evaluate the efficacy of spectinomycin or tetracycline for treatment of pharyngeal gonococcal infection or for prevention of postgonococcal urethritis, but it was possible to make inferences regarding the relative efficacy of these two regimens for these purposes as well.

MATERIAL AND METHODS

Design of Study

During a two-year period, from November, 1971, to October, 1973, patients seen at the Seattle-King County and Alameda County (Oakland) health departments were treated for uncomplicated genital or anorectal gonorrhea (or both) with one of three treatment regimens, which were assigned on an alternating basis, according to the day of the study. Men were given 2 or 4 g of spectinomycin hydrochloride, or oral tetracycline hydrochloride, 1.5 g initially followed by 0.5 g four times daily, for a total dose of 9 g. Women were assigned to the same dose of oral tetracycline hydrochloride on one day out of three, or to 4 g of spectinomycin hydrochloride on the remaining two days out of three. Because of the high failure rate for pharyngeal gonococcal infection in homosexual men given spectinomycin, soon after this study began, the clinics elected to treat all homosexual men assigned to spectinomycin therapy with the 4-g dose.

Patients were requested to return within five to eight days after completing treatment. During the return visit, repeat specimens were obtained for the isolation of *N. gonorrhoeae*, and patients were questioned about interval sexual re-exposure and about side effects of treatment.

Diagnostic Procedures

Specimens for culture were obtained with cotton swabs from the endocervix and anal canal of all women, and from the anal canal and pharynx of homosexual men. Although not required by the protocol, pharyngeal cultures also were occasionally obtained from women who had recently performed fellatio. Calcium alginate swabs were used to obtain specimens for Gram stain and culture from the anterior urethra of all men. Swabs were streaked immediately onto Thayer-Martin culture plates, which were incubated at 37°C in a 10 per cent carbon dioxide environment. Genital isolates were identified as *N. gonorrhoeae* on the basis of colonial morphology, Gram stain and oxidase reaction. Isolates from the pharynx and anal canal were further characterized by sugar-utilization tests.

Antibiotic-Susceptibility Testing

Colonies of *N. gonorrhoeae* were scraped from agar plates into medium containing 50 per cent trypticase soy broth and 50 per cent

horse serum, and were frozen at -70°C for later antibiotic-sensitivity testing. An agar dilution method² using chocolate agar medium containing Isovitalex supplement was employed to measure the minimum inhibitory concentration of spectinomycin and of tetracycline for pretreatment isolates of *N. gonorrhoeae* from every fifth patient and for all recoverable pretreatment and post-treatment isolates from patients with persistent or recurrent infection. Strains of *N. gonorrhoeae* with previously determined sensitivities to these antibiotics were included as controls.

Statistical Methods

Failure rates and rates of postgonococcal urethritis for different regimens were compared by chi-square test. The antimicrobial susceptibility of isolates from treatment failures was compared with that of randomly selected isolates by the Mann-Whitney test.

RESULTS

Results of Treatment

The results of treatment in Oakland and Seattle were comparable. The results of treatment of patients with anogenital gonococcal infection are summarized in Table 1. Of 2560 men and 1483 women who were treated for gonorrhea, 1825 (71.3 per cent) of the men and 1074 (72.4 per cent) of the women returned for follow-up examination within two weeks after initiation of tetracycline therapy or after the administration of spectinomycin. At three to 14 days after completion of therapy, failure rates for anogenital infec-

Table 1. Results of Treatment of Anal and Genital Infections with Spectinomycin (Spec) Intramuscularly and Tetracycline (Tet) by Mouth.

TREATMENT	PATIENTS TREATED	SEX	NO. OF FAILURES*	
			AT 3-14 DAYS†	TOTAL AT 5 WK
Spec:				
	2 g	M	39/704‡ (5.5)	46/727 (6.3)
	4 g	M	27/699‡ (3.9)	28/712 (3.9)
	1,016	F	29/742 (3.9)	29/748 (3.9)
Tet, 9 g	638	M	17/422§ (4.0)	20/436 (4.6)
	467	F	19/332 (5.7)	21/335 (6.3)

*No. of failures/patients followed, with % in parentheses.

†Re-exposure admitted by 10 (37%) of 27 men & by 16 (55%) of 29 women in whom treatment with 4 g of spectinomycin failed, by 16 (41%) of 39 men with failure with 2 g of spectinomycin, & by 4 (24%) of 17 men & 6 (32%) of 19 women with failure with tetracycline.

‡Includes 7 men who received 2 g & 38 who received 4 g of spectinomycin for anal infection, all of whom were cured.

§Includes 9 men with anal infection, 8 of whom were cured.

tion ranged from 3.9 to 5.7 per cent, with no significant differences in efficacy of the various regimens in men or women. The total failure rate for all men re-examined within five weeks was 6.3 per cent after 2 g of spectinomycin and 3.9 per cent after 4 g of spectinomycin (chi-square = 4.22, $P < 0.05$). The total failure rate for all women re-examined within five weeks was 6.3 per cent after 9 g of tetracycline and 3.9 per cent for 4 g of spectinomycin (chi-square = 3.01, $P < 0.1$). These represent maximal failure rates, since

possible reinfections are included with treatment failures. The percentage of patients with failure of therapy who admitted to sexual re-exposure was higher for those given the single-dose spectinomycin regimens (42 of 95) than for those given the multiple-dose tetracycline regimens (10 of 36, chi-square = 3.17, $P < 0.1$), suggesting that reinfection rather than relapse accounted for a higher proportion of spectinomycin recurrences.

The failure rate for oropharyngeal gonococcal infection after treatment with spectinomycin was higher for men (six of 11) than for women (one of 13, $P < 0.05$ by Fisher's exact test). Of four patients given tetracycline for oropharyngeal infection, two women were cured, and two men had persistent or recurrent infection.

The frequency of overt postgonococcal urethritis at the time of re-examination, as defined by the presence of an overt urethral discharge not containing *N. gonorrhoeae*, is shown for each treatment regimen in Table 2. The rates of postgonococcal urethritis observed probably represent underestimates because urinalyses were not performed and patients were not routinely re-examined two to three weeks after treatment at the optimal time for demonstrating this condition.²⁵ Nonetheless, postgonococcal urethritis was significantly less common after tetracycline (five of 398) than after 2 g of spectinomycin (46 of 659, chi-square = 17.7, $P < 0.001$) or after 4 g of spectinomycin (30 of 638, chi-square = 8.92, $P < 0.01$).

Correlation of Antibiotic Susceptibility with Treatment Results

Gonococcal isolates from Oakland and from Seattle did not differ significantly in susceptibility to tetracycline or spectinomycin, and in this study, isolates from men and from women did not differ in susceptibility to these antibiotics. The distributions of minimum inhibitory concentrations of each antibiotic for pretreatment isolates from every fifth patient and for pretreatment isolates from patients with failure of therapy at the two clinics are shown in Figure 1.

There was no significant correlation between re-

sponse to treatment with spectinomycin and gonococcal susceptibility to this agent. The mean minimum inhibitory concentration of spectinomycin was 15.7 μg per milliliter for isolates from 58 spectinomycin-treatment failures and 14.5 μg per milliliter for 535 isolates collected from every fifth patient ($P > 0.01$ by Mann-Whitney test). All isolates, including those recovered after treatment, were inhibited by 32 μg per milliliter or less of spectinomycin. Furthermore, gonococci recovered during the second year of the study were no more resistant to spectinomycin than

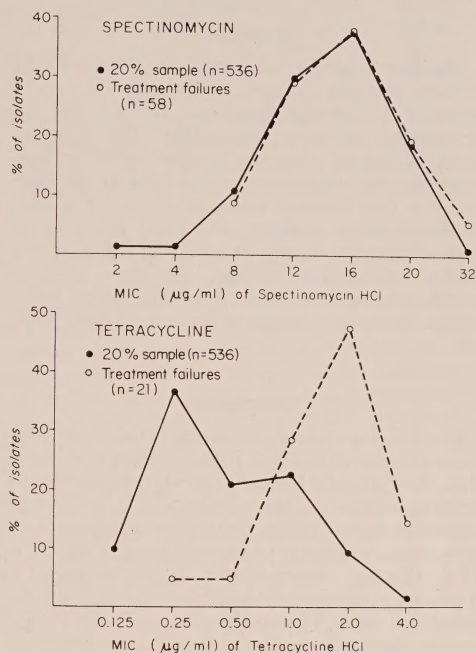


Figure 1. Distribution of Minimal Inhibitory Concentrations (MIC) of Spectinomycin Hydrochloride and of Tetracycline Hydrochloride for Every Fifth Pretreatment Isolate (20 Per Cent Sample) and for Pretreatment Isolates from Patients with Treatment Failures Who Denied Re-exposure.

Failure of spectinomycin treatment was unrelated to minimum inhibitory concentrations of spectinomycin, but that of tetracycline treatment was limited mainly to infections by gonococci having tetracycline minimum inhibitory concentrations $\geq 1.0 \mu\text{g}$ per milliliter.

those recovered during the first year, with no evidence of emergence of resistant strains as a consequence of increased spectinomycin use. The results of treatment with spectinomycin remained constant throughout the study.

Pretreatment isolates from patients whose subsequent tetracycline therapy failed were significantly

Table 2. Postgonococcal Urethritis after Treatment with Spectinomycin (Spec) Intramuscularly or Tetracycline (Tet) by Mouth.

THERAPY	MEN CURED OF URETHRAL INFECTION	PATIENTS WITH POSTGONOCOCCAL URETHRITIS	
		NO.	%
Spec:			
2 g	659	46	7.0
4 g	638	30	4.7
Tet, 9 g	398	5	1.3

* $P < 0.1$.

† $P < 0.005$.

more resistant to tetracycline hydrochloride than the isolates collected from every fifth patient during the study ($P < 0.0002$ by Mann-Whitney test). Although the number of isolates available from patients with failure of tetracycline treatment was small, it is possible to calculate the risk of treatment failure corresponding to the minimum inhibitory concentration of tetracycline for the infecting strain of *N. gonorrhoeae* by comparing the distribution of minimum inhibitory concentrations for all patients vs. those for treatment failures, and correcting for unequal sampling of the two groups.*

TOXICITY

The rate of adverse side effects was 1.3 per cent for patients receiving 2 g and 1.7 per cent for patients receiving 4 g of spectinomycin, and 4.4 per cent for patients receiving tetracycline. The most frequent complaint after the administration of spectinomycin was moderately severe pain at the injection site. Less common reactions attributed to spectinomycin were transient skin rash, pruritus, abdominal cramps, nausea or vomiting and dizziness. During tetracycline therapy, the most common complaints, nausea and vomiting, were severe enough to require change of therapy in three women.

DISCUSSION

In 1972 because of increasing gonococcal resistance to penicillin and a rising incidence of gonorrhea, the Center for Disease Control recommended increasing the dose of procaine penicillin G used to treat gonorrhea to 4.8 million units given intramuscularly at two sites, with 1 g of probenecid given by mouth. In 1974, this was recommended as the treatment of choice for uncomplicated gonorrhea¹ because the National Gonorrhea Therapy Monitoring Study³ showed it to be slightly more effective than the alternative single-dose ampicillin regimen. Since then two developments necessitate a re-examination of current gonor-

rhea-therapy guidelines. The first is the recognition that another sexually transmitted pathogen, *C. trachomatis*, is present in 20 to 60 per cent of patients with gonorrhea and is not eradicated by penicillin G, ampicillin or spectinomycin therapy. The extent to which this development should influence choice of therapy for gonorrhea depends upon the relative pathogenicity of *C. trachomatis* and *N. gonorrhoeae* and, hence, upon the relative importance of eradicating the two organisms in patients with both infections. *N. gonorrhoeae* is generally considered the more important pathogen, because of the complications that it can cause, particularly pelvic inflammatory disease,²⁶ disseminated gonococcal infection,²⁷ epididymitis and neonatal infections.²⁸ However, it has become apparent that *C. trachomatis* not only causes nongonococcal and postgonococcal urethritis and cervicitis²⁹ but now results in far more cases of ophthalmia neonatorum than the gonococcus,^{30,31} and it has recently been implicated as a possible cause of pelvic inflammatory disease,^{29,32} of epididymitis³³ and of eosinophilic interstitial pneumonia in infants.³⁴ Urethral chlamydial infection has also been associated with attacks of Reiter's syndrome.³⁵ Evidence that *U. urealyticum* causes many cases of chlamydia-negative gonococcal urethritis^{14,21} also argues against the routine use of penicillin or ampicillin for gonorrhea, at least in men.

The second development is the appearance of penicillinase (beta-lactamase)-producing strains of *N. gonorrhoeae*,⁶⁻⁹ predicted over a year ago.³⁶ The main reason for holding spectinomycin and tetracycline in reserve — namely, fear of selection of resistant variants — now also applies to the use of penicillin or ampicillin.

In view of these considerations, it seems less imperative to advise initial use of the procaine penicillin G regimen, which is the most toxic of the regimens recommended by the Center for Disease Control (causing pain, procaine reactions³⁷ and risk of anaphylaxis³⁸), as the treatment of choice for gonorrhea simply because it may be marginally more effective than the other single-dose regimens against strains of *N. gonorrhoeae* that do not produce penicillinase.

The present study was primarily an evaluation of the efficacy of spectinomycin and of tetracycline for treatment of gonorrhea, as well as an assessment of the risk of producing strains resistant to spectinomycin or tetracycline when these antibiotics are used as primary therapy for gonorrhea. Both drugs were quite effective for initial therapy of gonorrhea. The reported failure rates are inflated by inclusion of re-exposed patients. The results are somewhat encouraging in that patients with recurrent infection after spectinomycin treatment did not initially harbor spectinomycin-resistant organisms, and resistant strains did not emerge during therapy in 2187 patients followed after treatment. Similar results were obtained in two previ-

*If all isolates had been tested, the expected number of isolates at each level of minimum inhibitory concentration among all patients followed for three to 14 days after tetracycline therapy = the observed number of isolates at each minimum inhibitory concentration $\times$ [the total number of patients re-examined three to 14 days after tetracycline therapy (754) $\div$ number of isolates tested from every fifth patient (536) treated with spectinomycin or tetracycline throughout the study] = number of isolates observed at each concentration $\times 1.41$. The expected number of isolates at each level of minimum inhibitory concentration from patients with treatment failure at three to 14 days after therapy who denied re-exposure = the observed number of isolates from such patients at each level of minimum inhibitory concentration $\times$ [the total number with treatment failure at three to 14 days who denied re-exposure (26) $\div$ number of pretreatment isolates tested from such patients (16)] = the observed number at each minimum inhibitory concentration $\times 1.63$. The calculated failure rate at each concentration then = the expected number of isolates at each concentration in treatment failures $\div$ expected total number of isolates at each concentration from all patients followed after tetracycline therapy: $<0.5 \mu\text{g}$ = $1.63 \div 506 = 0.003$; $1.0 \mu\text{g}$ = $8.15 \div 169 = 0.05$; $2.0 \mu\text{g}$ = $11.4 \div 69.1 = 0.17$; $4.0 \mu\text{g}$ = $4.9 \div 11.3 = 0.43$.

ous co-operative studies of smaller groups of patients treated with spectinomycin.^{3,5} Nonetheless, it is quite likely that extensive reliance upon spectinomycin for initial therapy of gonorrhea would eventually lead to emergence of spectinomycin-resistant gonococci. High-level gonococcal resistance to the related drug, streptomycin, caused by chromosomal mutations affecting the 30S ribosome, occurred soon after the widespread use of streptomycin for treatment of gonorrhea in Europe. Sparling and his colleagues^{39,40} found that the rate of spontaneous *in vitro* ribosomal mutation causing spectinomycin resistance in gonococci was less common (about 1 per 10¹⁰ cells) than mutation causing streptomycin resistance (about 1 per 10⁹ cells), suggesting that the risk of selection of mutants *in vivo* may be lower with spectinomycin therapy than with streptomycin therapy.

Unfortunately, failure rates after tetracycline therapy rose sharply in the present study for infections caused by gonococci resistant to 1.0 μ g per milliliter of tetracycline, even when a dose of 2 g daily was given for four days. This can be considered a maximum daily dose of tetracycline, and unless more prolonged therapy would be more effective, it seems likely that a widespread shift to the use of tetracycline for initial therapy of gonorrhea, particularly in noncompliant patients, would lead to selection of isolates resistant to 1.0 μ g per milliliter of tetracycline and hence, would be a self-defeating maneuver. This pattern would be a reversal of the current trend in the United States toward decreasing gonococcal resistance to the tetracyclines.^{41,42} The level of resistance to tetracycline is now so high in some areas of Southeast Asia that the majority of men treated for acute gonococcal urethritis with 900 mg of minocycline over a four-day period do not respond to treatment (Harrison WO, et al: unpublished data). In short, gonococci appear capable of reaching levels of resistance to the penicillins, spectinomycin or the tetracyclines that are high enough to preclude outpatient therapy with these drugs.

Among the other alternative regimens for treating gonorrhea, erythromycin and sulfamethoxazole with trimethoprim have been studied most extensively. Erythromycin is highly active *in vitro* against *C. trachomatis* and has some activity against *U. urealyticum*, but unfortunately is not sufficiently active against prevailing strains of *N. gonorrhoeae*. In a recent Seattle study, approximately 25 per cent of cases of gonorrhea in men were treatment failures with erythromycin, 2 g daily for five days, after a 1.5-g loading dose (Brown ST: unpublished data). Erythromycin estolate was no more effective than erythromycin base in that study. Sulfamethoxazole with trimethoprim is active against *C. trachomatis*,²³ but is not highly active against *U. urealyticum*, and in a dose of 6 tablets once daily for three days is as effective as 4.8 million units of procaine penicillin G combined with 1 g of probenecid for gonococcal urethritis.⁴³ However,

treatment failure with the three-day regimen is correlated with gonococcal resistance to sulfamethoxazole.⁴³

In conclusion, indications for the choice of an antimicrobial for gonorrhea have become less clear-cut. No one regimen is entirely satisfactory. Although there is no immediate need to change current therapeutic guidelines, the use of spectinomycin or tetracycline as initial therapy in the doses employed in the present study seems at least as rational as the use of 4.8 million units of procaine penicillin G given intramuscularly or 3.5 g of ampicillin given by mouth, with 1.0 g of probenecid. Parenthetically, it should be noted that the 1.5-g loading dose of tetracycline appears to be unnecessary, provided the full four-day course of therapy is completed, since in patients given 500 mg four times daily for four days without a loading dose, serum levels of tetracycline develop after 24 hours that equal or exceed the peak attained after a 1.5-g loading dose; such patients appear to respond to therapy as well as those given the standard four-day regimen with a loading dose.⁴⁴

The direction of future research concerning gonorrhea therapy should include trials with cephalosporins resistant to gonococcal β lactamase, further study of the optimal dose of sulfamethoxazole with trimethoprim and perhaps combined use of more than one antimicrobial to prevent sequential development of chromosomally mediated, if not of plasmid-mediated, resistance. In the meantime, certain recommendations are clearly indicated: a test of cure after treatment is now, more than ever, essential to detect and prevent spread of resistant gonococci; and spectinomycin is the drug of choice for the treatment of patients who fail to respond to therapy with penicillin, ampicillin or tetracycline, because the low level of cross-resistance between spectinomycin and these other antibiotics does not appear to be clinically important. Tetracycline is clearly not indicated for re-treatment of penicillin or ampicillin failures, because moderate intrinsic cross-resistance between these antibiotics exists,⁴⁵ and β -lactamase-producing gonococci also appear to have relatively high levels of resistance to tetracycline.⁹

We are indebted to Mr. D. L. Walker and Ms. J. A. Hale for assistance in this study.

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AIDS



AIDS



AIDS



AIDS



**WHAT YOU SHOULD KNOW ABOUT
OUR HEALTH EMERGENCY...**

AIDS =

ACQUIRED IMMUNE DEFICIENCY SYNDROME

(not "GRID" or "gay plague" or "gay cancer")

IMMUNE SYSTEM =

Your body's way to fight off disease.

THEREFORE:

When you have AIDS, your body cannot fight off disease properly.

WHICH MEANS:

You are open to such serious illnesses as:

KS =

KAPOSI'S SARCOMA CANCER

PCP =

PNEUMOCYSTIS CARINII PNEUMONIA,

OR OTHER SERIOUS ILLNESSES.

By September 1982 there were 634 cases of AIDS in 23 states and 9 foreign countries. Last year at this time we only knew about 123.

50% OF ALL CASES ARE REPORTED FROM NEW YORK

40% OF ALL CASES ARE NOW DEAD

WATCH OUT FOR THESE SYMPTOMS

1. SWOLLEN GLANDS:

(Enlarged Lymph Nodes): With or without pain, usually in the neck, armpits, or groin.

2. PINK TO PURPLE FLAT OR RAISED BLOTCH OR BUMP:

These are without pain, on or under the skin, inside the mouth, nose, eyelids, rectum. They have appeared recently, usually small but gradually getting bigger. They may look like a bruise that doesn't go away. Usually they are harder than the skin around them.

3. WEIGHT LOSS:

Unexpected, and greater than 10 pounds in less than 2 months.

4. FEVER:

That has persisted for more than a week.

5. NIGHT SWEAT:

Periods of waking up drenched or sweaty over several weeks.

6. COUGH:

Persistent, often a dry cough that is not from smoking and has lasted too long to be from flu.

7. DIARRHEA:

Persistent and not explained by other causes.

ONE OR MORE OF THE ABOVE MAY BE CAUSE FOR CONCERN

1. GO TO A DOCTOR WHO IS UP-TO-DATE ON GAY HEALTH
2. TELL YOUR DOCTOR YOU ARE GAY.
3. IF YOU'RE NOT SURE HE KNOWS ABOUT AIDS—ASK HIM.
4. IF HE IS NOT FAMILIAR WITH AIDS, OR NOT SYMPATHETIC—GET ANOTHER DOCTOR.

IF YOU HAVE ANY QUESTIONS OR NEED A DOCTOR'S NAME:

CALL GAY MEN'S HEALTH CRISIS
HOTLINE: 685-4952

Not through simple social contact.

But current opinion points to something like a virus that MAY BE transmitted sexually.

THEREFORE: UNTIL WE KNOW BETTER IT MAKES SENSE THAT THE FEWER DIFFERENT PEOPLE YOU COME IN SEXUAL CONTACT WITH, THE LESS CHANCE THIS POSSIBLY CONTAGIOUS BUG HAS TO TRAVEL AROUND.

Have as much sex as you want—but with fewer people and with HEALTHY PEOPLE.

IF YOU DON'T KNOW IF YOUR PARTNER IS HEALTHY—ASK HIM DIRECTLY TO BE HONEST WITH YOU ABOUT HIS HEALTH.

PLAY FAIR YOURSELF:

IF YOU KNOW OR THINK OR SUSPECT THAT YOU HAVE ANY DISEASE YOU COULD GIVE TO SOMEONE ELSE, DON'T, RISK THE HEALTH OF OTHERS BY HAVING SEX. WAIT UNTIL YOUR DOCTOR TELLS YOU IT'S SAFE.

There is no conclusive evidence that any drug or sexual act causes AIDS. But until we know better, you might consider giving up drugs. I.V. drug is definitely a high-risk factor.

RECOMMENDATIONS—WHAT YOU CAN DO:

(This recommendation is made by New York Physicians for Human Rights—the organization of 175 gay doctors in New York, and also by the New York City Department of Health.)

We don't know yet what causes AIDS.

Until we do:

CUT DOWN THE NUMBER OF DIFFERENT MEN YOU HAVE SEX WITH. PARTICULARLY WITH THE MEN WHO ALSO HAVE MANY DIFFERENT SEXUAL PARTNERS.

HELP YOURSELF!

IF YOU HAVE ANY QUESTIONS:

CALL

GAY MEN'S HEALTH CRISIS HOTLINE

685-4952

Someone will call you back.

If you want to receive the free Newsletter of Gay Men's Health Crisis, which contains the latest available information on AIDS, or send a contribution, write to:

**G.M.H.C.
Box 274
132 West 24th Street
New York, New York, 10011**

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AIDS

ACQUIRED IMMUNE DEFICIENCY SYNDROME

1. What is it?

2. Who is
affected?

3. Can it be
prevented?

4. What are the
Symptoms?

5. Where can I
go for help?

In the summer of 1981, the medical community in Boston became aware of reports from New York and California of two rare and potentially serious illnesses that were affecting otherwise healthy, young homosexual men. Since that time, these illnesses have also affected exclusively heterosexual men, women and people outside of the United States. Individuals with these illnesses have been diagnosed and treated in Boston since the recognition of the problem.

Information concerning this condition, now called **AIDS**, has been widespread throughout the popular press. Unfortunately, many misconceptions and some incorrect information have arisen concerning the physical, emotional and spiritual issues that relate to these new diseases. As concerned health care providers, in conjunction with the Office of the Mayor of Boston, we have prepared this brochure to help make available the most accurate, clear and up-to-date information on AIDS. We hope that it will help the gay, bisexual and straight communities deal more effectively with this syndrome.

WHAT IS AIDS AND WHO IS AFFECTED?

AIDS is a shortened version of Acquired Immune Deficiency Syndrome, a group of illnesses and symptoms which, taken together, form a similar medical picture. **The immune system** is made up of parts of the body which function to fight infection and which may also help the body rid itself of abnormal cells that might produce cancer. With AIDS, the normal functioning of the immune system is severely impaired and individuals may become vulnerable to infections and other illnesses which rarely affect the average person. Two of the diseases that are often involved are: Kaposi's sarcoma (KS), which is an unusual form of cancer, and *Pneumocystis carinii* pneumonia (PCP), an uncommon infection of the lungs.

Seventy-five percent (75%) of those individuals who are affected by AIDS have been homosexual and bisexual men. It is important to realize, however, that some women, some individuals outside of the United States and some heterosexual men have also developed AIDS. Thus, AIDS should not be considered a "gay plague" or a "gay cancer" but rather a **public health issue**. It has so far affected at least two people per day since 1981 for a total of more cases than Legionnaire's disease, Toxic Shock and the Tylenol product tamperings combined. Approximately 40% of those persons affected by AIDS have died. All of

us — gay, bisexual and straight — should be aware of and concerned about this growing problem.

As yet, it is unknown exactly why one person develops AIDS, while another person does not. Some scientists think that there may be an infectious process which causes AIDS, while other scientists are less certain. During this period of scientific uncertainty, it seems prudent that all of us consider those lifestyle factors that help or hinder us from maintaining a normally-functioning immune system. It is hoped that this type of personal and community-wide activity will diminish the likelihood that others will become affected by AIDS.

PREVENTING AIDS

No one risk factor has been definitively implicated in producing AIDS. It seems, however, that the number of different sexual partners that one has may be an important factor. If there is an infectious process that causes AIDS, then having many different partners probably increases the risk of exposure. It also seems wise that all of us observe some positive health practices that will optimize the operation of our immune defenses. These include: abstaining from intravenous drug use and heavy "recreational" drug use in general, maintaining healthy nutritional and hygienic practices, and seeking regular medical care from an **informed** practitioner.

So far, no one has been able to further define other risk factors that are specific for AIDS. However, if you have more than one sexual partner, we advise that you get regular medical check-ups which screen for sexually transmitted disease. These illnesses, if they occur frequently, may be a contributing factor. Other factors being studied include: the use of nitrite drugs ("poppers"), anal sex, "rimming" (oral-anal sex), swallowing semen and poor nutrition. We do not know, as yet, their role, if any, in producing the AIDS picture. Once again, be aware that the frequency of sexual activity does not appear to be a factor in acquiring AIDS, but instead it is the **number of different** sexual partners that may be relevant.

WHAT ARE THE SIGNS OF AIDS?

AIDS is a complex and serious illness that develops gradually over time. Any one of the signs listed below (or more than one) is a cause for concern, but it is not a reason to panic. The important point is to **take stock of your own health**. Seek medical attention if

you suspect that one or more of the following symptoms may be occurring in you:

- Multiple or enlarging lymph nodes (swollen glands) in the groin, neck or armpit (although there are many other conditions which can cause this problem, most of which are not serious)
- Weight loss of 10 pounds or more in two months that does not appear to be related to dieting or increased physical exercise
- Fever or night sweats, with or without shaking chills, that appear unrelated to a cold or viral infection and which do not appear to be improving
- Persistent diarrhea
- Purplish bumps or spots on the skin, inside of the mouth, nose or anus that do not heal promptly
- Severe fatigue (extending over more than one week) which persists despite having your usual periods of rest and in the face of maintaining your normal diet
- Shortness of breath unassociated with exertion, especially in association with a dry cough unrelated to smoking

Be aware that there is no **one** symptom or sign of AIDS and no **single** screening test that can tell you if you have AIDS. However, many different illnesses can occur in the person with AIDS and these can be diagnosed and treated. We should all be alert to the signs described above in ourselves, our friends and our sexual contacts. As is true in most illnesses, **prompt recognition and treatment** is helpful. Therefore, be alert to the potential signs of AIDS and seek medical help if you suspect they may be occurring.

WHAT TO DO IF YOU HAVE A QUESTION ABOUT AIDS

If you have one or more of the potential warning signs of AIDS, or if you have a general question concerning AIDS, there are a number of resources that can provide help. For general questions call:

Community Epidemiology Department	
Boston City Hospital	(617) 424-5916
Fenway Community Health Center	(617) 267-7573
Lesbian and Gay Hotline	(617) 426-9371
National Gay Task Force Hotline	1-800-221-7044

Sometimes it is difficult for gay men, who appear to be at an increased risk of acquiring AIDS, to get the best health care. In some instances, we are reluc-

tant to notify our medical providers of our sexual preferences because we are uncertain about their attitudes. In other cases, it is our providers who are not well versed in the diagnosis and treatment of illnesses related to gay sexuality. For whatever reason, it is essential to discuss AIDS and to be evaluated for it by someone who is **knowledgeable** about the issue and aware of your sexual preference and your sexual activity. If you cannot do this with your current medical care giver, call one of the above numbers for a referral to a physician or clinic where you can be open about your sexual preference.

COPING WITH AIDS

The recognition of AIDS as a national health issue is causing controversy in the gay community and at the same time stirring many of us to do some important self-searching. Sometimes, in the course of these reflections, the AIDS issue can lead us to inappropriate thoughts and feelings of fear, panic and guilt. If you have any of these thoughts and feelings, it is important to realize that **you do not have to cope with them alone**. The Gay and Lesbian Counseling Services of Boston (617-542-5188) and the Fenway Community Health Center (617-267-7573) are prepared to offer appropriate guidance and referrals.

Moreover, we should all be aware that a national effort is underway to find the cause and treatment of AIDS. In New England, there are many resources for gay, bisexual and straight people who are concerned about these issues. One such resource is the AIDS Action Committee (617-267-7573), a grass roots group, organized through the Fenway Community Health Center, which is dedicated to education, outreach, advocacy and consciousness-raising. They provide discussion groups and support. No one should feel alone with his or her feelings or medical problem. If you are concerned, seek help today.

HOW YOU CAN HELP

If you wish to join forces with those persons working on the AIDS issue, one very easy and critical act is to send a copy of this brochure to your Congressional Representative and Senators. In your cover letter, ask their support for federal funding for research into the cause and treatment of AIDS. More specifically, seek the continued and increased funding of the Centers for Disease Control and the National Institutes of Health.

To find out the name of your Representative, call the Massachusetts Gay Political Caucus at

(617) 262-1565 or the League of Women Voters at
(617) 357-5880. Address your letters to:

Senator _____
Senate Office Building
Washington, D.C. 20510

Representative _____
House Office Building
Washington, D.C. 20515

ABOUT THIS BROCHURE

This material has been prepared by the Mayor's Ad Hoc Committee on AIDS, the Fenway Community Health Center and the Gay and Lesbian Physicians of New England (GALPONE). The project has been funded by the Trustees, Boston Health and Hospitals.

The **Mayor's Ad Hoc Committee on AIDS**, formed by the Mayor's Liaison to the Gay and Lesbian Community in response to the AIDS issue, is made up of representatives of the Centers for Disease Control, the State Department of Health, the Boston Department of Health and Hospitals, the Fenway Community Health Center and representatives of the gay and lesbian community.

The **Fenway Community Health Center** provides a comprehensive primary care program which integrates its commitment to the greater Boston gay and lesbian community along with its basic commitment to the local elderly and young adult population. The clinic is also involved in extensive infectious disease research.

The **Gay and Lesbian Physicians of New England (GALPONE)** is an association for support, educational outreach and recreation.

For further information on these sponsors or for additional copies of this brochure, please contact:

The Mayor's Ad Hoc Committee on AIDS
Room 608, Boston City Hall
Boston, MA 02201/(617) 725-4849

The Fenway Community Health Center
16 Haviland Street, Boston, MA 02115
(617) 267-7573

GALPONE
P.O. Box 971, Back Bay Annex
Boston, MA 02117/(617) 482-6874

SPECIAL THANKS

The sponsors of this brochure gratefully acknowledge the unique contribution to this effort on the part of Ken Mayer, MD, research director of the Fenway Community Health Center and Hank Pizer, physician's assistant at the Fenway Community Health Center.

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The cooperation of the National Association of Enterostomal Nurses

* * * * *

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Fred Moore
714 N.E. 17 Court
Fort Lauderdale, Fla., 33305
(305) 763-6365 or 463-7895

or The Metropolitan Community Church, 330 S.W. 27 St, Fort Lauderdale, Fla.
(305) 462-2004

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"There are times when it can be a drag, but basically the ileostomy is a problem only if you let it be."

"Now I live a modified normal life."

"Even though I'm not too good at it, I ride dirt bike and have a lot of fun doing it."

"My lover and I are going on a bike trip with 175 other gay bikers."

"I make no effort to hide my ostomy; no second thoughts about wearing a brief bikini . . . if anyone doesn't like it that's too bad."

"I work out at a gym regularly and am completely open about my ostomy (walk around naked, use showers and sauna)."

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"Due to surgery, I suffered sexual impairment due to nerve damage. I have had sex a few times since surgery and none since 1978."

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"I had my ostomy early in life so that my adult life has not been impaired, with the exception of sexual fulfillment."

"The ostomy operation for gay men involves the loss of a sexual organ . . . even for those who don't use it for anal sex."

"I have run into problems with my appliance. I now am able to refuse to let them bother me for the most part."

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"I've felt quite alone with my problem."

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Another kind of closet: Gay ostomates

At UOA's 20th Annual Conference in Atlanta last August, it was resolved that, "The United Ostomy Association will never turn its back on any ostomate regardless of age, race, religion, ethnic background, sex or sexual preference."

It is timely, therefore, that minority groups encompassed by this resolution, make their presence known. One already has. *The Advocate*, a nationwide semi-monthly newspaper for homosexual ("gay") men and women, recently ran a story about gay ostomates. Originally written for *The Advocate* by Lenny Giteck, it is condensed and presented to you here. (Reprinted with permission from *The Advocate*, P.O. Box 5847, San Mateo, CA 94402. Copyright 1982, Liberation Publications Inc.)

Lenny Giteck, author of this article, has an extensive background in journalism that started when he earned a Bachelor's degree from San Francisco State. He was an assistant editor for *The Advocate*, and also a staff writer for the *San Francisco Examiner*. Giteck has several projects currently under way. Although he is not an ostomate, two of his relatives are, one of whom is only 11 years old. A third relative, who died in 1980, became an ostomate in 1935, which was perhaps one of the earliest ostomies in the United States.

Bill Etnyre, as a result of this story's run in *The Advocate*, started an informal, nationwide, mutual support network for gay ostomates. Men from all over the United States and Canada have replied; Lesbian ostomates are encouraged to come forward so that their story can also be told and so that they can also participate in the mutual support network. Now, Etnyre is planning a research project to study, in great detail, both the experiences and needs of gay and Lesbian ostomates. Those interested in either the support network or the research project are asked to contact Bill Etnyre of Social Workers Northwest at 2408 10th Ave. E. in Seattle, Washington 98102, or call 206/325-8224.

By Lenny Giteck

"About a year-and-a-half ago, when my lover and I were down at the Russian

River (north of San Francisco), I decided to go skinny dipping. I went into the water and really enjoyed myself. But when I got out, a guy yelled at me, 'Hey, do you know you've got a milk carton attached to your side?' I usually have a comeback for everything, but I couldn't say a word. Although it was embarrassing at the time, I've been able to laugh about it since." — Bill Etnyre

Etnyre, a 35-year-old social worker living in Seattle, did not have a milk carton attached to his side. Nine years ago, surgeons performed an ileostomy on this gay man — who was suffering from severe ulcerative colitis — in order to save his life. What was hanging from his side was an "appliance" (a neoprene bag) that collects the fecal matter that his body produces.

Etnyre is not alone. According to statistics from United Ostomy Association, 1.5 million men and women in the United States and Canada are ostomates. An additional 110,000 undergo ostomy surgery every year.

Ostomy surgery can pose special problems for lesbians and gay men. Therefore, to better understand it, we learned a lot from Dr. Richard Cazen, a gastroenterologist in San Francisco:

Ostomy can pose a problem if the person isn't near a bathroom. "I've been in private aircraft," Gary (a 48-year-old gay ostomate from Los Angeles) relates, "where I sat there wondering if we were going to arrive at our destination soon, or if I was going to wind up fertilizing the fields below. My worst fear is getting trapped with people in an elevator for several hours."

Sex can be problematic as well. One sexual activity becomes impossible for many people who undergo ostomy surgery; obviously, when your anus is surgically closed, you can no longer be on the receiving end of anal intercourse. Many male ostomates also experience difficulty having erections after their surgery. In some cases, surgeons attempting to cut out all traces of cancer have been forced to sever nerve endings that relate to sexual functioning. In most instances, however, impotence appears to result more from psychological causes than from physical ones. When physical causes are the problem, doctors can now

implant an air pump or semi-stiff rods into a man's penis to enable him to have erections. (These procedures have had mixed results.) When psychological factors are the problem, counseling can help.

Gary, who has had his ileostomy for many years, went through a difficult period of sexual adjustment after a number of men responded negatively to his condition. He recalls: "I became so concerned and uptight about how my sex partners would react, that I couldn't function in bed. I thought it might be a physical problem because of the surgery, but my doctors determined that it was just stress and nervousness. I finally went to a sex therapist and that really helped. I realized that I was still a worthy human being, and that I couldn't let other people put me down. I just don't take it personally any longer."

Today, Gary has a good, active sex life. Nonetheless, the question of when and how to tell someone about the ileostomy remains a dilemma. Do you tell a prospective sex partner in the bar? After you go home? Do you try to cover the bag during sex? "When I go to bed with someone," Don confides, "I do wear my shorts. Even though the bag is black and you can't see any of the contents, I don't think it's particularly aesthetic. If the shorts bother the other person, I'll wrap a bandage around my abdomen and cover the bag that way." Other ostomates don't try to hide the bag.

The process of self acceptance differs from ostomate to ostomate.

Fred, a 60 year old ostomate living in Florida, remembers, "I was scared to death of the operation, but my biggest worry was how my lover would take it. At that time we'd been together for 16 years, and I knew it would mean an enormous change in our lives. It was hard for him to deal with at first, but eventually he came to accept it very well." They're still together four years later.

UOA volunteers visit those who are about to undergo the operation. "The guy who visited me," Etnyre says, "was about my age, was in robust health, was active in sports and rode a motorcycle. It was great to talk to him. I realized I'd still be able to swim, ski and go backpacking." He laughs: "Actually, being an ostomate is sort of convenient when you're out in the wilderness. It's much easier to just pull off the trail, dig a hole in the ground and empty your bag."

Etnyre: "I was really determined not to let it get me down or stop me. But when I thought about the alternative — death — it wasn't so bad." Don has similar feelings. "Sometimes when I'm at the gym, I feel a little sad that I can't just jump into the sauna or Jacuzzi with everyone else. But then I realize how lucky I am there's an operation that could save my life."

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Another kind of closet: Gay ostomates

At UOA's 20th Annual Conference in Atlanta last August, it was resolved that, "The United Ostomy Association will never turn its back on any ostomate regardless of age, race, religion, ethnic background, sex or sexual preference."

It is timely, therefore, that minority groups encompassed by this resolution, make their presence known. One already has. *The Advocate*, a nationwide semi-monthly newspaper for homosexual ("gay") men and women, recently ran a story about gay ostomates. Originally written for *The Advocate* by Lenny Giteck, it is condensed and presented to you here. (Reprinted with permission from *The Advocate*, P.O. Box 5847, San Mateo, CA 94402. Copyright 1982, Liberation Publications Inc.)

Lenny Giteck, author of this article, has an extensive background in journalism that started when he earned a Bachelor's degree from San Francisco State. He was an assistant editor for *The Advocate*, and also a staff writer for the *San Francisco Examiner*. Giteck has several projects currently under way. Although he is not an ostomate, two of his relatives are, one of whom is only 11 years old. A third relative, who died in 1980, became an ostomate in 1935, which was perhaps one of the earliest ostomies in the United States.

Bill Etnyre, as a result of this story's run in *The Advocate*, started an informal, nationwide, mutual support network for gay ostomates. Men from all over the United States and Canada have replied; Lesbian ostomates are encouraged to come forward so that their story can also be told and so that they can also participate in the mutual support network. Now, Etnyre is planning a research project to study, in great detail, both the experiences and needs of gay and Lesbian ostomates. Those interested in either the support network or the research project are asked to contact Bill Etnyre of Social Workers Northwest at 2408 10th Ave. E. in Seattle, Washington 98102, or call 206/325-8224.

By Lenny Giteck

"About a year-and-a-half ago, when my lover and I were down at the Russian

River (north of San Francisco), I decided to go skinny dipping. I went into the water and really enjoyed myself. But when I got out, a guy yelled at me, 'Hey, do you know you've got a milk carton attached to your side?' I usually have a comeback for everything, but I couldn't say a word. Although it was embarrassing at the time, I've been able to laugh about it since." — Bill Etnyre

Etnyre, a 35-year-old social worker living in Seattle, did not have a milk carton attached to his side. Nine years ago, surgeons performed an ileostomy on this gay man — who was suffering from severe ulcerative colitis — in order to save his life. What was hanging from his side was an "appliance" (a neoprene bag) that collects the fecal matter that his body produces.

Etnyre is not alone. According to statistics from United Ostomy Association, 1.5 million men and women in the United States and Canada are ostomates. An additional 110,000 undergo ostomy surgery every year.

Ostomy surgery can pose special problems for lesbians and gay men. Therefore, to better understand it, we learned a lot from Dr. Richard Cazen, a gastroenterologist in San Francisco:

Ostomy can pose a problem if the person isn't near a bathroom. "I've been in private aircraft," Gary (a 48-year-old gay ostomate from Los Angeles) relates, "where I sat there wondering if we were going to arrive at our destination soon, or if I was going to wind up fertilizing the fields below. My worst fear is getting trapped with people in an elevator for several hours."

Sex can be problematic as well. One sexual activity becomes impossible for many people who undergo ostomy surgery; obviously, when your anus is surgically closed, you can no longer be on the receiving end of anal intercourse. Many male ostomates also experience difficulty having erections after their surgery. In some cases, surgeons attempting to cut out all traces of cancer have been forced to sever nerve endings that relate to sexual functioning. In most instances, however, impotence appears to result more from psychological causes than from physical ones. When physical causes are the problem, doctors can now

implant an air pump or semi-stiff rods into a man's penis to enable him to have erections. (These procedures have had mixed results.) When psychological factors are the problem, counseling can help.

Gary, who has had his ileostomy for many years, went through a difficult period of sexual adjustment after a number of men responded negatively to his condition. He recalls: "I became so concerned and uptight about how my sex partners would react, that I couldn't function in bed. I thought it might be a physical problem because of the surgery, but my doctors determined that it was just stress and nervousness. I finally went to a sex therapist and that really helped. I realized that I was still a worthy human being, and that I couldn't let other people put me down. I just don't take it personally any longer."

Today, Gary has a good, active sex life. Nonetheless, the question of when and how to tell someone about the ileostomy remains a dilemma. Do you tell a prospective sex partner in the bar? After you go home? Do you try to cover the bag during sex? "When I go to bed with someone," Don confides, "I do wear my shorts. Even though the bag is black and you can't see any of the contents, I don't think it's particularly aesthetic. If the shorts bother the other person, I'll wrap a bandage around my abdomen and cover the bag that way." Other ostomates don't try to hide the bag.

The process of self acceptance differs from ostomate to ostomate.

Fred, a 60 year old ostomate living in Florida, remembers, "I was scared to death of the operation, but my biggest worry was how my lover would take it. At that time we'd been together for 16 years, and I knew it would mean an enormous change in our lives. It was hard for him to deal with at first, but eventually he came to accept it very well." They're still together four years later.

UOA volunteers visit those who are about to undergo the operation. "The guy who visited me," Etnyre says, "was about my age, was in robust health, was active in sports and rode a motorcycle. It was great to talk to him. I realized I'd still be able to swim, ski and go backpacking." He laughs: "Actually, being an ostomate is sort of convenient when you're out in the wilderness. It's much easier to just pull off the trail, dig a hole in the ground and empty your bag."

Etnyre: "I was really determined not to let it get me down or stop me. But when I thought about the alternative — death — it wasn't so bad." Don has similar feelings. "Sometimes when I'm at the gym, I feel a little sad that I can't just jump into the sauna or Jacuzzi with everyone else. But then I realize how lucky I am there's an operation that could save my life."

The New Epidemic

Immune Deficiency, Opportunistic Infections, and Kaposi's Sarcoma

By Jeanne Allen
Grace Mellin

In the past year over 600 cases involving Kaposi's sarcoma and/or serious opportunistic infections (*Pneumocystis carinii* pneumonia in particular) were reported to the Centers for Disease Control (CDC)(1). Forty percent of the patients in the reported cases died, touching off anxiety among the segment of society hardest hit by these diseases—homosexual and bisexual men living in urban areas. Reports of the diseases have not abated; in fact, increasing numbers are being reported every day. Although Kaposi's sarcoma (KS) and *Pneumocystis carinii* pneumonia (PCP) have been known to scientists for many years, the diseases had heretofore affected only a limited population of compromised, susceptible people.

In the present epidemic, 608 cases of Kaposi's sarcoma and opportunistic infections were reported to CDC. One hundred eighty-three cases (30 percent) were of Kaposi's sarcoma only; 309 (51 percent) were *Pneumocystis carinii* pneumonia only; 44 (7 percent) were both KS and PCP; and 72 (12 percent) were patients with other opportunistic infections. Males constituted 573 (94 percent) of these cases, and of these men, 403 were homosexuals, 54 were bisexuals, 86 were heterosexuals. In 30 cases, sexual preference was unknown. All 35 of the female cases were heterosexual(1).

Overall, CDC reports that of patients for whom drug use information was known, 60 percent of the heterosexual men and 62 percent of the women used intravenous

drugs at some time as compared to 12 percent of the homosexual men(1). The age range of those affected was 15 to 60 years(1). Eighty-eight percent of the reported cases seem to be clustered geographically—New York (50 percent), California (22 percent), Florida (7 percent), New Jersey (6 percent), and Texas (3 percent)(1).

AIDS—A Puzzling Syndrome

Some people consider Kaposi's sarcoma and serious episodes of opportunistic infections to be manifestations of a single problem—acquired immunodeficiency syndrome (AIDS). The immunodeficient syndrome is often evident among young homosexual men. There is no known cause or cure.

AIDS has surfaced, so far, in four groups: people who have KS; people who have opportunistic infections; people who have generalized enlargement of their lymph glands, loss of weight, and weakness; and people who have a wasting syndrome in which they exhibit weight loss and inability to work and function properly(2). These symptoms cause them to seek medical care, and AIDS becomes apparent when the diagnostic test results are evaluated.

Although etiology of AIDS is unknown, life-style factors seem to be involved and the agent appears to be infectious. Currently, epidemiologists and others investigating the syndrome believe that it can be spread through sexual contact and blood products—and there may be other means of transmission not yet identified(2). Although it seems that the syndrome does not readily spread in the general population, people who handle blood may be at risk. At this time, however, CDC has not identified health care workers to be at increased risk; no cases

of AIDS have been reported in heterosexual nurses or physicians(1).

AIDS may result in a continuous deterioration of the immune system; initially, small tumors may appear on the skin, more tumors may develop, and eventually the patient may succumb to an infectious agent that the body's defenses can no longer resist. On an experimental basis, "biologic response modifiers" (which are thought to have anticancer and antiviral effects and which, if given at the right time, may stimulate the immune response) are being used with some AIDS patients. One such drug is interferon(2).

KS—A Rare Cancer

Until recently, Kaposi's sarcoma was known in this country as a rare malignant neoplasm of unknown etiology that caused multiple violaceous vascular lesions, primarily on the lower extremities. It affected men 10 times more often than women; men of some Mediterranean stocks, particularly Ashkenazi Jews and Italians, 60 to 70 years



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old, were thought to be at highest risk. Yearly incidence of Kaposi's sarcoma was estimated to be only 2 to 6 cases per 10 million population(3,4). Although the lesions were diffuse and ulcerating, the illness was considered treatable and rarely resulted in fatalities. Survival in this older population group was 8 to 13 years(5).

The new outbreak of KS differs from the classic pattern. It is unusual to see such a high number of cases among young, previously healthy men. Although the prototypical violaceous lesions are present, they are likely to be discrete and nodular and are not confined to the lower extremities(6). Since the lesions are not itchy or painful, initial discovery often is accidental. The clinical course of cases in the new outbreak is aggressive and can lead to lymphadenopathy, visceral lymph node involvement, and tumors on internal organs. The mortality rate has also significantly changed—the mean survival rate in one study was 15 months(7).

In some ways, the clinical course of recent U.S. cases resembles the pattern of KS seen in Uganda, where the disease accounts for nine percent of all cancers. Other features of the disease in the equatorial African environment are: average age of onset is less than 20 years; the cancer affects adult males 13 times more often than women; and, in 10 percent of the cases, the clinical course includes visceral lesions and

general lymphadenopathy. If lymphadenopathy is present, the survival time is three years(7,8).

The etiology of KS is still unknown, but the fact that it is endemic in certain areas suggests genetic, infectious, and environmental factors. Cytomegalovirus (CMV) infections have been suspected because CMV can produce degrees of immunosuppression(9). Up to 94 percent of homosexual men (as compared to up to 47 percent of heterosexuals) have antibody titers that reflect past or current active CMV infections(9). CMV has been found in close serologic association to KS(6).

Kaposi's sarcoma has also been reported in persons who have been clinically immunosuppressed for transplant operations.

Immunogenetic studies done on 32 men who had KS showed a significant increase in a common HLA phenotype—DR-5(10). The use of amyl nitrite and butyl nitrite among young, sexually active homosexuals has been viewed as significant, both because these drugs have been found to be immunosuppressive and because nitrites have been implicated as carcinogens(6).

PCP—An Opportunistic Infection

Pneumocystis carinii is a ubiquitous protozoan. Under normal conditions, it does not cause disease in humans, requiring, for example, some immunologic or nutritional

compromise to affect a host. PCP can be contagious and is spread by the respiratory route(11). Until now, almost all cases of PCP occurred in patients who had primary congenital immunodeficiencies or hematogenous cancers, or in patients who were receiving immunosuppressive chemotherapy. Recently, however, several young, previously healthy homosexual and bisexual men were treated for multiple episodes of PCP, extensive mucosal candidiasis, and severe viral infections(12). Even more recently, Kaposi's sarcoma and/or opportunistic infections, including PCP, were found among 38 Haitians in the United States; none of 23 Haitian males questioned said that they were homosexual, and only 1 out of 26 who were asked gave a history of drug abuse(1,13). And in July 1982, CDC reported three cases of PCP in patients who had hemophilia A with no other underlying disease. A fourth such case was reported in September 1982(1). These men were long-term recipients of Factor VIII concentrate; all were heterosexuals, and none had a history of drug abuse(14).

Again, these outbreaks of PCP manifested in young, otherwise healthy men who gave no history of immunologic dysfunction. When tested, however, they were anergic and lymphopenic; they had an acquired T-cell defect, but their B-cell defenses were intact(15).

The clinical course of PCP



The lesions associated with the current epidemic of Kaposi's sarcoma are usually discrete and nodular and are found on all parts of the body as well as on mucous membranes.

Patient Information: Questions and Answers about KS and AIDS

Q: I'm confused by all the abbreviations and technical terms. Please explain KS, PCP, AIDS, and opportunistic infections.

A: KS stands for Kaposi's sarcoma, a rare malignant tumor. PCP is a label for what can be severe pneumonia—*Pneumocystis carinii* pneumonia. AIDS stands for Acquired Immunodeficient Syndrome (or State). This deficiency in the body's defense system is also referred to as GRID (Gay Related Immunodeficiency), SAID (Sexually Acquired Immunodeficient Syndrome), and ACIDS (Acquired Cellular Immunodeficient Syndrome).

Opportunistic infections are caused by agents that do not normally cause disease in humans but which may take hold because of the body's lowered resistance to infection.

Q: Why did I get AIDS/PCP/KS? What made me more susceptible?

A: No one can yet be certain about causes. Although many investigators now believe that AIDS is transmitted by a virus, exposure alone does not cause the disease. This suggests a combination of such possible risk factors as genetic predisposition, high cytomegalovirus (CMV) antibody titers, abuse of intravenous drugs, use of amyl/butyl nitrites, many sexual partners, and many episodes of sexually transmitted diseases. Although most cases have appeared in homosexual and bisexual men, the disease is not limited to them. There is a small, but growing number of cases of AIDS/KS/PCP in persons who report no homosexual behavior or drug abuse. Cases involving hemophiliacs lend support to the theory of viral transmission via blood and blood products.

Q: What are the symptoms to watch for?

A: Most patients have reported feeling constantly tired and that they had lost their normal sense of well being. Swollen glands can be easily felt in the neck, armpits, or groin. Night sweats and repeated fevers, weight loss of more than ten pounds in two months, and noticeable shortness of breath unrelated to physical exercise are other possible signs. Purplish patches that appear anywhere on the skin surface should be investigated by a physician.

Q: What does KS actually look like?

A: Lesions are usually purplish in color and can appear anywhere on the body. They can be either flat or slightly raised above the skin, and they are not itchy or painful.

Q: Once I am diagnosed as having AIDS, will I always have it?

A: Health professionals have only been aware of AIDS for a short time, so it is difficult to determine the long-term course of the disease. At this time, those with AIDS should be treated as if they were permanently immunodeficient.

Q: If I have AIDS, will I definitely get KS or PCP?

A: No. Your chances, however, are greater than those of people who don't have AIDS, and you must be careful to avoid further lowering your resistance and exposure to opportunistic infections. KS and opportunistic infections, as well as other diseases that your body could once have resisted, may now present a threat.

Q: What do you mean "be careful"? Does this mean I have to change my lifestyle?

A: The decision of how the diagnosis will affect your lifestyle is left to you. Guidelines and suggestions can be given, but once you are aware of the risks, it is your choice whether or not you want to modify your behavior. Some suggestions are: select your sexual partners from a small group of people whom you know well and who have all agreed to limit their sexual contacts to people within the group; abstain from sex with persons who have known infections. Careful hygiene is always important in sexual activity and this includes avoiding any combination of oral sex and anal sex that would risk introduction of fecal microorganisms into the mouth. It would be wise to use a condom during anal sex, preventing introduction of disease-causing microorganisms into the urethra and the easily damaged rectal mucosa. Regular medical followup is essential, even if you feel well. Of course, you should notify your health care provider immediately if you have symptoms.

These guidelines are based on our best knowledge of factors apparently associated with AIDS, but there is no set of actions that will guarantee that the disease will not occur or progress.

Q: Must I take medicines? If so, for how long?

A: People who have AIDS may be put on trimethoprim and sulfamethoxazole (Bactrim or Septra), an antibacterial combination that has been used to try to prevent PCP. But long-term results of this preventive regimen are not yet known.

Dispensed in tablet form, Bactrim or Septra is best absorbed when taken one hour before or two hours after meals. Take the medicine with a large glass of water and drink plenty of fluids each day (a quart or more). Side effects may include skin rashes, sore throat, fever, mouth sores, and sensitivity to light. Notify your health care provider if they occur. Also, be aware of your usual urine output and notify your health care provider if it suddenly declines. Avoid exposure to the sun and also avoid sunscreen preparations containing PABA—they may cause a skin reaction.

The National Gay Task Force has installed a special "hot line" that people can call to obtain up-to-date information about AIDS. The toll free number (800) 221-7044 can be called from anywhere in the continental United States, except New York State Monday through Friday from 12 noon to 6 PM, and in New York call 212/892-6016.

starts insidiously, usually beginning with symptoms of mild upper respiratory infection—fever, chills, sore throat, mild nonproductive cough, and/or headache. It may be three to eight months before diagnosable symptoms occur. The condition may then become more severe, with increasing dyspnea on exertion, pain on inspiration and cough, a higher fever that is at times accompanied by drenching night sweats, weight loss, tachypnea and air hunger, anxiety, and cyanosis(16,17).

At this stage, deterioration can be rapid, with death occurring within days or weeks(17). The parasites have now proliferated in the lungs, forming cystic packs of two to eight organisms that gradually occupy all the air space. The results are impaired diffusion and severe hypoxemia with normal or slightly elevated PCO₂(16). Thus, the patient slowly suffocates.

On autopsy, the lungs are found to be completely full of the organism. Little evidence of phagocytosis is seen; the mucoid-covered packets resist it. The organism does not infiltrate the lung cells(15).

In June, CDC reported that the case fatality ratios for homosexual men who had PCP with onset in 1980 and 1981 were 85 percent and 45 percent, respectively, and 67 percent and 41 percent, respectively, for heterosexual men(18).

A combination of trimethoprim and sulfamethoxazole (Bactrim, Septra), PO or IV, is the treatment of choice. Pentamidine isethionate (Lomidine), IM, is used when there is no response to the Bactrim. Since pentamidine is a research drug and must be obtained from the CDC, requests for it alerted CDC to the increased number of pneumocystis cases(16,19).

Supportive measures include oxygen therapy with assisted or controlled ventilation to maintain PO₂ at 60-70 and treatment of secondary or concomitant bacterial or other opportunistic infection. Complications of the disease include pneumothorax and rib fractures, azotemia, hypoglycemia, alterations in liver functions, and, often, severe secondary infections(16). These infections can include oral and systemic candidiasis, ulcerating herpes simplex lesions, and cryptococcal

meningitis. In addition, a significant number of patients develop such side effects from the drugs as renal toxicity, hypotension, hypoglycemia, and pulmonary fibrosis(20).

Nursing Care Experiences

On our medical/surgical unit at Roosevelt Hospital, we have seen

11 people with AIDS. Two patients in this group also had Kaposi's sarcoma, and both were subsequently discharged, three died from PCP. Several of the AIDS victims have been readmitted with progressively deteriorating conditions; one with KS was readmitted for high fever and gastric distress. All 11 patients were homosexual or bisexual men,

A Case History

Mr. N, 37 years old, was admitted on December 20, 1981. He had a history of upper respiratory illness, malaise, unusual fatigue, anorexia, weight loss, chills, and fever. Initially, Mr. N attributed these symptoms to exposure to photographic chemicals and poor ventilation in his new work environment. His symptoms persisted, he sought medical help. He was seen by several physicians but he had no relief from the symptoms. When he was admitted, his past medical history revealed only a history of hepatitis in 1965. He acknowledged that he was bisexual and used amyl nitrate as a recreational inhalant.

Since Mr. N was dyspneic, he received supportive oxygen therapy (40 percent Ventimask), Tylenol, alcohol sponge baths and, at one point, a cooling blanket, were needed to control his fever. We checked his vital signs at least qid and sought to make him comfortable with fresh linens and lotion for his dry skin. The dietitian visited, and foods were ordered to entice his flagging appetite. We also encouraged his friends and family to bring in favorite foods and items that would make his room more homey and festive. They brought pictures and holiday decorations; they even decorated his IV pole with Christmas garlands and ornaments.

Mr. N was diagnosed as having PCP, and his medical workup showed cytomegalovirus in the blood and urine, anemia, and lymphopenia. Although he received IV Bactrim, his fever did not abate. In fact, his temperature rose during each Bactrim administration. Physicians diagnosed these episodes as a drug fever and he received Tylenol every four hours to prevent cyclical spiking. Mr. N developed oral and systemic candidiasis, which was treated with ketoconazole (Nizoral), Nystatin, and viscous lidocaine hy-

drochloride 2 percent (Xylocaine). Since he was having difficulty eating, he was given soft foods and liquids; we gave careful oral care and monitored his intake and output.

Mr. N was a Catholic who had gradually fallen away from regular practice of his religion. He was worried that he would die and wanted to be at peace, spiritually. At his request we arranged for a priest to visit.

When Mr. N's respiratory status deteriorated, his oxygen was changed to 40 percent aerosol. Because of Mr. N's diaphoresis and inability to take adequate food and fluids by mouth, IV therapy was increased. On New Year's Day, pentamidine isethionate was obtained from CDC, and after Mr. N consented, IM adjunctive therapy was started. His apical pulse and blood pressure were taken immediately before the drug was given and one hour afterward to watch for tachycardia or hypotension. For three days thereafter, Mr. N's condition seemed improved, but then his symptoms worsened.

On January 7, Mr. N's chest x-ray showed almost complete white-out of both lung fields, and he was transferred to ICU and put on a respirator. Mr. N was alert, oriented, and terrified about what was happening to him. The nurses tried to spend more time with him and make him as comfortable as possible. The nurses in ICU relaxed the visiting regulations and allowed his family and friends to be with Mr. N whenever possible.

Pentamidine therapy was discontinued but Bactrim and anti-Candida therapies were maintained. Mr. N developed GI bleeding, which was treated with IV cimetidine (Tagamet). His level of consciousness deteriorated, and on January 10, following resuscitation from two respiratory arrests, Mr. N died.

and they had varying levels of knowledge about their illness. They expressed fear ("Am I going to die?"), denial (refusal to discuss their illness), anger ("Gay-related, gay-related! Don't heterosexuals get sick any more?"), and acceptance.

Our hospital's committee on prevention and control of infection, concerned about possible transmission of AIDS to staff and other patients, decided that patients with a confirmed or tentative diagnosis of AIDS must be placed on special precautions regarding blood, oral secretions, urine, and stool. Because of concern about these patients' compromised immune defenses, we have been careful not to assign them to beds near patients who have infectious diseases.

We think that it is important for health care providers to keep abreast of the new information about these diseases. But in our investigation of PCP, KS, and opportunistic infections, we found interdisciplinary communication to be haphazard. Within our institution there were separate outreach/support and immunologic research projects underway, each without knowledge of the other, although directed at the same patient population. Nursing information generated on our unit was poorly communicated to other units where there were patients who had PCP, KS, or AIDS. Thus, other units could not benefit from our prior experience with these diseases.

The same situation seems to prevail elsewhere. When we called other hospitals about AIDS patients, no one seemed to know who the appropriate resource person was, or even who might direct us to that person. At one hospital where a conference had been held on AIDS, even those who might have been interested in participating seemed to know little about it.

Education of the at-risk population is urgent. In New York City, AIDS has started receiving media attention. More significantly, the gay community, through its network of communication and publications, has given priority to reporting information about AIDS and is closely monitoring relevant research. This population is clearly alarmed. Homosexuals have been

encouraged to be alert for signs of immune dysfunction and to seek health screening and care on a regular basis. But patients who are not part of the gay subculture are at a disadvantage. It would be helpful if providers developed lists of possible local support groups and information centers to share with all affected patients.

Assisting the patients in arranging continuing support after hospital discharge will encourage the patients' compliance with ongoing monitoring of their health. On our unit we see patients when they are readmitted and are able to assess their ongoing emotional needs. One such patient, who had AIDS and who had been extremely anxious on his first admission, returned because of continued malaise and fatigue. On readmission he was more accepting of his prognosis and was able to discuss his concerns with the staff. He had made profound changes in his life. Because of the chronicity of his illness, he had resigned from his job. He had also accomplished the difficult task of informing family and friends about his illness and the possibility of his shortened life expectancy. This patient found that he relied for his major support on a select group of his closest friends, rather than on relatives or an organized support program. Another patient told us that he was abstaining from sexual intercourse because he feared he would spread his illness to friends. We accepted each patient's decisions, gave emotional support to the patients and their significant others, and shared what information we had regarding the diseases in question.

Continuity of patient contact enhances the therapeutic relationship and adds to the body of knowledge available within and outside the health care system. It gives to patients a sense of contributing to one another's welfare, bolsters self-esteem, and lends some meaning to their suffering.

Research continues. At our hospital, researchers are doing quarterly follow-up assessments of 100 healthy homosexual volunteers for five years. Some gay organizations are raising money to help fund research projects related to AIDS. The National Cancer Institute has

pledged an extra \$1.25 million to study AIDS. Researchers are looking at possible relationships between immune deficiency, infection, and the development of cancer(2). During the past six months, 75 to 80 cases of AIDS have been reported to CDC each month. A special CDC task force of 100 people is now working on the problem(2).

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of sexual intercourse. Coitus can also become painful for women who suffer from cystitis (an inflammation of the bladder). Clearly, in such cases, medical treatment is indicated.

Vaginal sensitivity can develop as a reaction to chemicals used in contraceptive or douching preparations. In such cases, the use of the offending substances has to be discontinued. (As a rule, vaginal douching is unnecessary and may be harmful.)

If another cause of pain during coitus is a thinning of the vaginal walls in older women, the condition can be improved by hormonal treatment. Occasionally, some women may develop an unpleasant sensitivity of the clitoris, either because some secretions have accumulated under the foreskin of the clitoris or because the head of the clitoris has been overstimulated by the male partner. (This misguided practice may be the result of bad advice given in some marriage manuals.)

VENEREAL DISEASES

Sexual intercourse can be among the healthiest and most enjoyable experiences in life. Unfortunately, it is sometimes also allowed to become the source of needless misery, suffering, and even death. For example, our society today is still perpetuating and indeed aggravating a serious health problem that could have been eliminated a long time ago: the venereal diseases.

The vague and poetic term "venereal diseases" (literally, diseases attributed to Venus) is a euphemism for those contagious diseases that are transmitted through intimate physical contact, especially sexual intercourse. There

of course, many other diseases that can be transmitted by intimate contact with another person, such as the common cold, smallpox, tuberculosis, and other infectious diseases. Nevertheless, the so-called venereal diseases have been singled out as a distinct group because they are almost always contracted by close contact with a diseased sexual partner, and they usually first affect the sex organs by which this contact has been made.

The various venereal diseases produce very different symptoms but are transmitted the same way: They are caused either by viruses or by germs which thrive in the warm, moist inner surfaces of the body (particularly in the mucous membranes of the sex organs, mouth, and rectum). Outside of this favorable environment, they quickly die. For this simple reason, they cannot be picked up from toilet seats, doorknobs, or similar objects (although in the very rare cases some venereal diseases have been picked up from used towels, underwear, and other clothing). On the other hand, sexual intercourse provides ideal conditions for all of these microorganisms to be transmitted from one person to another. It is very well possible to become infected with several venereal diseases at the same time. While all of them can be cured, there is never an immunity against them. One can catch all venereal diseases again and again.

In the United States today, the most common and most dangerous venereal diseases are gonorrhea and syphilis. Both have a long history dating back to ancient times, and for thousands of years nothing could be done about them; they not only remained incurable, but ever-increasing sexual taboos eventually made them unmentionable. Finally, in 1910, the first at least partially effective cure for syphilis was discovered (with Salvarsan, an arsenical compound also known as "606"). Still, it was not until the arrival of penicillin in the 1940s that successful treatment of both syphilis and gonorrhea could be assured. Nevertheless, it is now apparent that this scientific breakthrough was not enough. There also has to be a drastic change in society's attitudes. In the past, when venereal diseases were poorly understood, they were

often seen as a moral rather than a medical problem. Intolerant minds called them "the wages of sin" and believed them to be the just punishment of debauchery. According to this philosophy, "nice" people did not get venereal diseases. It was also believed that a young person should not learn too much about them. Fear and ignorance were supposed to keep him chaste. (There was even the opinion that a successful cure could only encourage sexual license and would thereby undermine the moral health of society.) Compared to this danger the threat to people's physical health seemed somehow less important. These and similar misguided views often led to irresponsible public policies for which we are paying a heavy price today. Moreover, in recent years the invention of new contraceptive methods has reduced the use of condoms which had always helped somewhat in the prevention of venereal diseases. Finally, inefficient self-treatment by ignorant patients in some parts of the world has contributed to the development of new and stronger strains of gonorrhea which, in our age of increasing travel, are quickly spread to other countries. These and other factors have now produced what can only be called a venereal disease epidemic.

54/3 This epidemic is hurting young people most of all. The greatest increase in reported infections is among teenagers. Because of inadequate education, they are often totally ignorant about the causes and symptoms of venereal disease. Consequently, many of them do not realize that they have become infected and thus may infect others. Some young people are also too afraid or embarrassed to seek treatment because they do not want their parents to find out that they had sexual intercourse. (In a number of states, a physician is not allowed to treat a minor for venereal disease without informing the parents.) However, the consequences of an untreated venereal disease are much worse than any momentary family crisis.

Fortunately, free tests and treatment for venereal disease are offered by departments of health in most cities. Such treatment always remains completely confidential. Nevertheless, every doctor is required by law to report any case of venereal disease to the appropriate public health agency. This is necessary in order to trace contacts who might also need treatment. Naturally, their privacy is protected as well.

The fight against venereal disease can still be won if everybody cooperates with those measures. Obviously, people who have become infected must immediately stop having sexual intercourse until they are cured. They should also ask their partners to get tests and, if necessary, treatment. Beyond such individual contributions, however, the most important task is this: Our society as a whole must make sure that every sexually mature person, including teenagers, learns the facts about venereal disease.

Fortunately, in recent years much progress has been made toward that goal. For example, the National Community Service Corps has established a national hotline that can be called toll-free from anywhere in the United States. It is operated mostly by teenagers who are well informed about the venereal diseases and who can give advice as to where to go for free examination and treatment in each community. This telephone service is available during regular business hours. The number is (800) 523-1885.

Remember:

- Venereal diseases are dangerous.
- You can have a venereal disease without having any symptoms. 55/5
- You can have several venereal diseases at the same time.
- Venereal diseases can easily be cured if treated early.
- Free tests and treatment are offered by your local department of health.
- All treatment for venereal diseases remains completely confidential.
- Self-treatment is ineffective.
- You can catch venereal diseases again and again.

The following paragraphs provide some basic information about the different venereal diseases.

54/1

Gonorrhea, also popularly known as "the clap" or "the drip," is by far the most common venereal disease today. It is caused by a bacterium, the gonococcus, which is transmitted from one person to another through the mucous membranes of the sex organs, the mouth, or the rectum. (Outside of these warm and moist areas, the gonococcus quickly dies.) It is therefore nearly impossible to contract the disease from toilet seats, doorknobs, towels, and other such objects.

GONORRHEA

gonococcus

Recent article in New England Journal of Medicine says it is possible but can survive only in pus of infected person (7-22-79)

Symptoms

An infection of the sex organs with gonorrhea (in the case of genital intercourse) will usually be noticed by a male within 2-10 days because of a sudden burning sensation when urinating. At the same time, a thick, green-yellowish discharge ("the drip") will appear at the opening of the penis. In females, on the other hand, the infection can often go unnoticed for quite some time. The early symptoms may be the same as in the male: a burning sensation and a discharge. However, it is also possible that no symptoms appear at all. In this case, the female may not realize that she is infected. (Thus, she may not only risk later complications for herself, but also unknowingly transmit the disease to others.)

54/1

An infection of the throat with gonorrhea (in the case of oral intercourse) may produce symptoms similar to those of an ordinary sore throat ranging from scratchiness to severe pain upon swallowing. However, very often there are no symptoms at all.

An infection of the rectum with gonorrhea (in the case of anal intercourse) may cause itching, burning, or bleeding, a yellowish discharge and pain when defecating. These symptoms are often mistaken for a simple case of diarrhea or hemorrhoids, and the necessary treatment may be delayed for this reason. Unfortunately, sometimes there are no symptoms at all.

If gonorrhea remains untreated, its early symptoms may disappear by themselves, but it will then spread inside the body and cause internal abscesses, arthritis, and sterility (the latter especially in women). The baby of a mother who has gonorrhea may be infected during its birth. In order to prevent possible eye infections with gonococci, the eyes of newborn children are routinely treated with a special solution.

Diagnosis

Gonorrhea can be properly diagnosed only by a physician, primarily by means of a bacterial culture which is taken from the infected area, i.e., the sex organs, the throat, or the rectum.

Treatment

Gonorrhea is a serious disease requiring the earliest possible treatment. Fortunately, modern medicine has made such treatment simple, fast, and effective. If treated early, gonorrhea can usually be cured within a few days with penicillin. Occasionally, some other medication is indicated. A successful cure does not mean immunity, however. A person can catch gonorrhea again and again.

Prevention

The only certain way to prevent an infection with gonorrhea is to avoid sexual intercourse with an infected partner. However, since the disease is so widespread today and symptoms may sometimes be unnoticeable or absent, this advice almost amounts to a demand for complete sexual abstinence. Those who do engage in genital or anal intercourse can at least partially protect themselves by wearing a condom, and by urinating and washing with soap and water immediately afterwards. In the case of coitus, some protection is also provided by spermicidal foams and jellies which are introduced into the vagina. Perhaps gargling with some antibacterial mouthwash after oral intercourse is not entirely useless either. Still, all of these measures are, at best, only marginally effective. Sexually active females are therefore well

54/2

→ 54/11

advised to have vaginal cultures taken at regular intervals. Males as well as females who engage in oral intercourse should also ask for a throat culture. A rectal culture is necessary in cases of anal intercourse. In any case, it may be useful to remember at least this: Someone who has an exclusive sexual relationship with only one partner is in less danger of catching gonorrhea than a person who changes partners frequently.

SYPHILIS

Syphilis (or lues), also popularly known as "the shit" or "bad blood," is the most dangerous venereal disease. Although it is not nearly as common as gonorrhea, it is by no means rare. Syphilis is caused by a bacterial organism, the spirochete, which is transmitted from one person to another through intimate physical contact, particularly the touching together of the moist inner body surfaces during sexual intercourse. Outside the human body, the spirochete cannot survive more than a few seconds. It is therefore practically impossible to contract syphilis from toilet seats, bath tubs, towels, bed linens, or other such objects. Neither can the disease be transmitted through the intact skin. However, the spirochete, which may be present in the mucous membranes, the saliva, semen, or blood of an infected person, can enter any cut or even slight skin abrasion of his sexual partner. *

Symptoms

The first symptom of a syphilitic infection is a painless ulcer or sore (chancre) which appears within ten to ninety days at the point where the spirochete entered the body. Depending on the kind of sexual intercourse, this can be anywhere: on or near the sex organs, the mouth, the rectum, or some other area. (The ulcer may be large and obvious or small and hardly noticeable.) If it should appear inside the vagina or rectum, it might easily go undetected. * Unfortunately, sometimes there is no outward symptom at all. In any case, the ulcer heals itself after a while. An infected person may thus gain the false impression that he is cured. In reality, however, the disease has now entered its second stage.

At the second stage of syphilis, the spirochetes have entered the bloodstream and thus spread through the whole body. The result is a rash, which usually appears 3-6 weeks after infection. This rash may take almost any form and may cover a small or large surface of the skin. In some cases, no rash may appear at all. Both the rash and the primary ulcer are infectious. There may also be a loss of patches of hair.

After the rash has disappeared, the disease enters its third stage which may last from a few months to several years. There may be no symptoms at all for quite a long time. However, this stage is the most dangerous of all because the disease may now suddenly attack various areas inside the body, destroying normal tissue and causing serious heart disease, blindness, paralysis, brain damage, and even death.

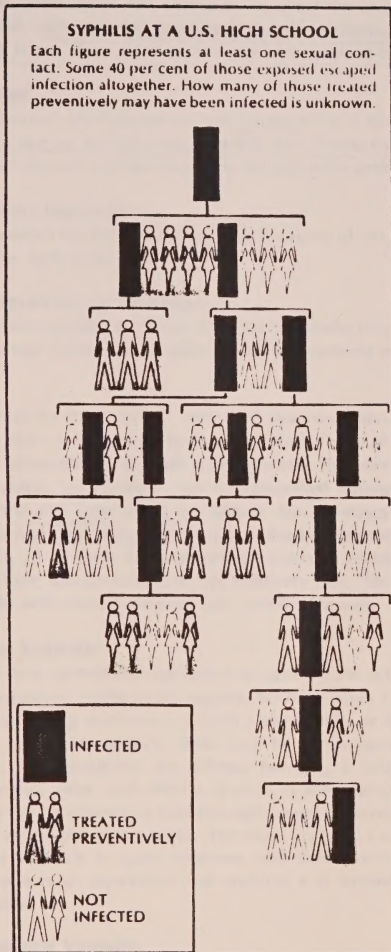
Syphilis can be transmitted to a baby before its birth through the mother's bloodstream. Because of this danger, expectant mothers need to have a blood test for syphilis early in the pregnancy.

Diagnosis

A diagnosis of syphilis can be made only by a doctor, usually by means of a blood test.

Treatment

Syphilis is a very dangerous disease which requires the earliest possible treatment. Fortunately, it is easily curable today, although any damage that has occurred before treatment is started cannot be repaired. The usual treatment consists of a series of penicillin shots. Occasionally, some other medication may be indicated. In order to insure success, follow-up blood tests are necessary. Successful treatment does not result in immunity. A person may catch syphilis again and again.



Note that the disease is spread by both heterosexual and homosexual contact. In the case cited here, the total number of individuals is 63. Of these, 44 had only heterosexual contact; 16 had only homosexual contact; 3 had both heterosexual and homosexual contact. (Source: Newsweek, Jan. 24, 1972)

Prevention

The only certain way to protect oneself against syphilis is to avoid sexual intercourse with an infected partner. However, since there may be no noticeable symptoms and people may therefore have the disease without knowing it, the best advice for any sexually active person is to have regular blood tests (one every 3-6 weeks). Such tests, together with proper treatment (where necessary), are offered free by public health clinics in most cities.

Wearing a condom during genital or anal intercourse and urinating and washing with soap and water immediately afterwards also offer at least partial protection, as will the use of vaginal contraceptive foams or jellies.

There are some other, less common, venereal diseases which deserve to be mentioned. Although they are found mainly in tropical countries, it may be useful to know about them in our age of increasing travel.

SOME TROPICAL VENEREAL DISEASES

Chancroid

The chancroid, also known as "soft chancre," is a bacterial infection which results in one or several large, painful, and destructive ulcers within a few days. The disease can be effectively treated with antibiotics.

Granuloma Inguinale

This is another bacterial infection which causes ulcers. It can also be treated effectively with antibiotics.

Lymphogranuloma Venereum

An infection caused by a virus. The disease produces an ulcer and a swelling of the lymph nodes in the groin. Effective treatment is possible.

In addition to the "classic" venereal diseases, there are numerous other diseases that can be spread by sexual contact. Some of them are very serious, such as salmonellosis, typhoid fever, amoebic dysentery, and hepatitis. Infectious hepatitis, for example, can be transmitted through fecal contamination during oral-anal intercourse (anilingus). Some viruses causing hepatitis appear in semen and saliva and thus can also be transmitted sexually. Needless to say, in all of these cases immediate medical attention is essential. Fortunately, these serious infections are relatively rare. The following paragraphs deal only with more common, less serious diseases.

OTHER DISEASES THAT CAN BE SPREAD BY SEXUAL INTERCOURSE

Monilial Vaginitis

Women may sometimes experience an upset in the ecological balance of the many organisms living in the vagina. Such an upset can result from vaginal douching, taking antibiotics or birth control pills, or from a variety of other causes. As a consequence, there may be an overgrowth of a yeast called monilia. The symptoms are itching, burning, a whitish discharge with a characteristic odor, and often a dryness of the vagina. It is also possible to transmit the condition to a man through sexual intercourse, causing an inflammation at the tip of the penis. The man, in turn, can reinfect the woman. Monilial vaginitis is quite common and does not have the same serious consequences as gonorrhea and syphilis. It is treated with locally applied medication.

Trichomonal Vaginitis

The trichomonas vaginalis, a single-cell organism, is present in the urethra and bladder of many men and women. While it usually does not produce any symptoms in males, it may, under certain conditions, cause problems in women who may develop a burning sensation when urinating and a vaginal discharge which is whitish, foamy, and has a characteristic odor. There may also be some reddening and swelling of the vaginal opening. The condition

VD

A CHECKLIST OF SYMPTOMS

It is very well possible to suffer from gonorrhea and syphilis without having any symptoms. Every sexually active person should therefore have periodic medical tests. However, if there are symptoms they may appear in the following parts of the body:

The Whole Body:

A slight fever accompanied by an overall feeling of sickness may be a symptom of either *syphilis* (second stage) or *gonorrhea* of the throat.

The Skin:

Itchy raised areas or red bumps which look like mosquito bites but do not cure themselves may be caused by *scabies*. Also, *syphilis* chancres can appear anywhere on the body where contact has been made. A body rash may be a symptom of *syphilis* (second stage). A syphilitic rash is likely to extend to the palms of the hands and the soles of the feet.

The Scalp:

A sudden loss of patches of hair may be a symptom of *syphilis* (second stage).

The Mouth:

A harmless looking "cold sore" may actually be a *syphilis* chancre.

The Throat:

A sore throat may be caused by *gonorrhea* after oral intercourse. However, in most cases gonorrhea of the throat does not show any symptoms.

The Penis:

A painless open sore may be a *syphilis* chancre. Burning sensations and a white or yellowish discharge may be symptoms of *gonorrhea* or *nonspecific urethritis*. Small, painful blisters which appear and then heal themselves only to recur again may be *herpes*. As long as the blisters are present, the virus is very contagious. Small, cauliflower-shaped warts may be *venereal warts*.

The Vulva and Vagina:

Chancres appearing on the major or minor lips may indicate *syphilis*, although this disease rarely shows symptoms in the female sex organs. A whitish discharge and abdominal cramps may indicate *gonorrhea*. Vaginal discharges are more likely to be caused by *monilia* or a *trichomonas* infestation. The vulva may also be affected by *herpes*, *venereal warts*, and *crabs*.

The Anus:

Small cauliflower-shaped warts may be *venereal warts*. A discharge of blood or mucus on feces, especially if accompanied by rectal itching, may be a symptom of anal *gonorrhea*. However, at this site the disease most often does not show any symptoms. The anal area and rectum may also develop a *syphilis* chancre after anal intercourse.

is treated with oral medication and has to involve both sexual partners. This is necessary because a man who harbors the trichomonas organisms, while usually developing no symptoms of his own, may very well retransmit the condition to a woman. Trichomonas infestations are common. They do not result in the same complications as gonorrhea and syphilis.

Venereal Warts

Venereal warts are the result of a viral infection. Since this infection usually occurs during sexual intercourse, the warts appear on or near the sex organs or anus of both men and women. Treatment is relatively easy and effective.

Herpes Progenitalis

Cold sores or herpes are due to a viral infection which appears at the various openings of the body, particularly around the mouth and nose. An infection of these areas can, of course, occur without sexual contact. However, herpes of the sex organs are caused by a different virus and are transmitted from one person to another by sexual intercourse. The symptoms are painful ulcers on or around the male or female sex organs or the anus. The ulcers may hurt for several weeks, then gradually heal themselves and disappear. Unfortunately, there may also be recurrent attacks. There is no simple and effective treatment. Nevertheless, men and women who discover these ulcers on their sex organs or anus should see a doctor in order to rule out other more serious diseases.

Nonspecific Urethritis

Nonspecific urethritis is the name given to some infections which may result in an inflammation sometimes producing symptoms similar to those of gonorrhea: a discharge and discomfort when urinating. However, the condition is less serious than gonorrhea and can often also be successfully treated within a few days.

Crab lice, also known as "crabs," live and breed mostly in pubic hair and thus can be transmitted from one person to another by close sexual contact. In rare instances, the transfer may also be through infested clothing or bed linen. In any case, their presence will soon be noticed since they cause a persistent itching in the pubic area. The condition is treated with a prescription item, Kwell (ointment, lotion, or shampoo), or with A-200 Pyrinol, which is available without prescription. Before using any medication, a hot bath and extensive washing with soap are important. Wearing clean clothing afterwards will prevent reinfestation. Clothing and linen which may be infested should be dry cleaned or laundered and dried in a hot dryer.

CRAB LICE

The itching of scabies is caused by a tiny mite which burrows through the skin. The mite can be transferred from one person to another by sexual and other physical contact as well as through infested clothing or bed linen. As in the case of crab lice, the infestation is treated with locally applied lotions (Kwell).

SCABIES

Reference and Recommended Reading

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GAY MEN'S HEALTH CRISIS—CIRCUS MADISON SQUARE GARDEN—APRIL 30, 1983
To order tickets complete form and mail to GMHC, Box 274, 132 W. 24th Street, N.Y., N.Y. 10011 or phone (212) 807-7517. To charge include Mastercard or Visa number and expiration date. Make checks payable to GMHC. Tax deductible to the extent permitted by law. Include stamped self-addressed envelope.

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Volunteer Name: _____

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Address: _____ Day phone: _____

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Dear Friend,

As you may have already heard, the Gay Men's Health Crisis has bought out all 17,597 tickets for the Saturday night performance on April 30, 1983, of the Ringling Brothers Parnum & Pailey Circus at Madison Square Garden. We hope that you will participate in making this the biggest gay event of all time.

Our aim is to raise at least \$150,000. We have been working in many areas of education and patient services concerned with AIDS. Our organization, now with over 300 volunteers, is stretched to the breaking point. We need more money to carry on and we feel that this circus benefit will help us toward our goal of becoming more financially independent.

In the past six months, GMHC has been responsible for almost all of the information that has come to the community about AIDS--through our Newsletter (25,000 copies), our Health Recommendation Brochure (250,000 copies), our Hotline (now fielding up to 100 calls a day), our two Open Forums, our Media Relations Committee (which has worked with the press to present sensitive treatment of our epidemic). We have met with local and national political figures, we have awarded almost \$50,000 in grants to research in New York hospitals, and we have tried to protect our community against unsuitably prepared research studies and improper medical and hospital treatment.

But most of all we have instituted a very ambitious program of Patient Services--to help our friends and lovers who may be ill with AIDS. We have trained Crisis Intervention Counselors to stay with newly diagnosed patients: we have established individual and group therapy support systems: and we have created a network of Buddies who visit and do chores for those too ill.

We are proud of this work, and we hope that you are too. We are growing very quickly, as is, unfortunately, this epidemic. For us to continue this growth, we need your continued support.

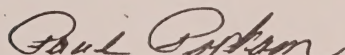
Tickets for our Circus are available at \$25, \$15, and \$10. They make wonderful holiday and birthday gifts. They make wonderful presents. If you want to put a group of friends together and order a minimum of 20 tickets in any one price category, we'll hold a block of seats for you and you can continue to buy additional seats in that block until Feb. 1.

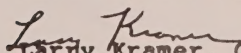
In addition, we have three special categories of tickets: be a Lion (Benefactor) for \$500, a Tiger (Patron) for \$250, or a Teddy Bear (Sponsor) for \$100. Holders of these special tickets will be invited to pre-Circus festivities.

We ask that you send us your order quickly. Although we anticipate that we are going to sell out, this is a mammoth undertaking for us. Avoid disappointment by getting your order in to us now. These early funds can also be put to use by GMHC that much more quickly.

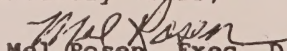
All tickets are tax-deductible to the extent provided by law. And all contributions to GMHC are tax-deductible too. You can charge your tickets to Visa or Mastercharge. You can order tickets by telephone, calling us at (212) 807-7517. Or you can mail us your order on the blank attached to the enclosed flyer.

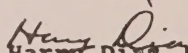
We need your money and we need your support. Please help us all help all of us. Thank you.


Paul Popham, President

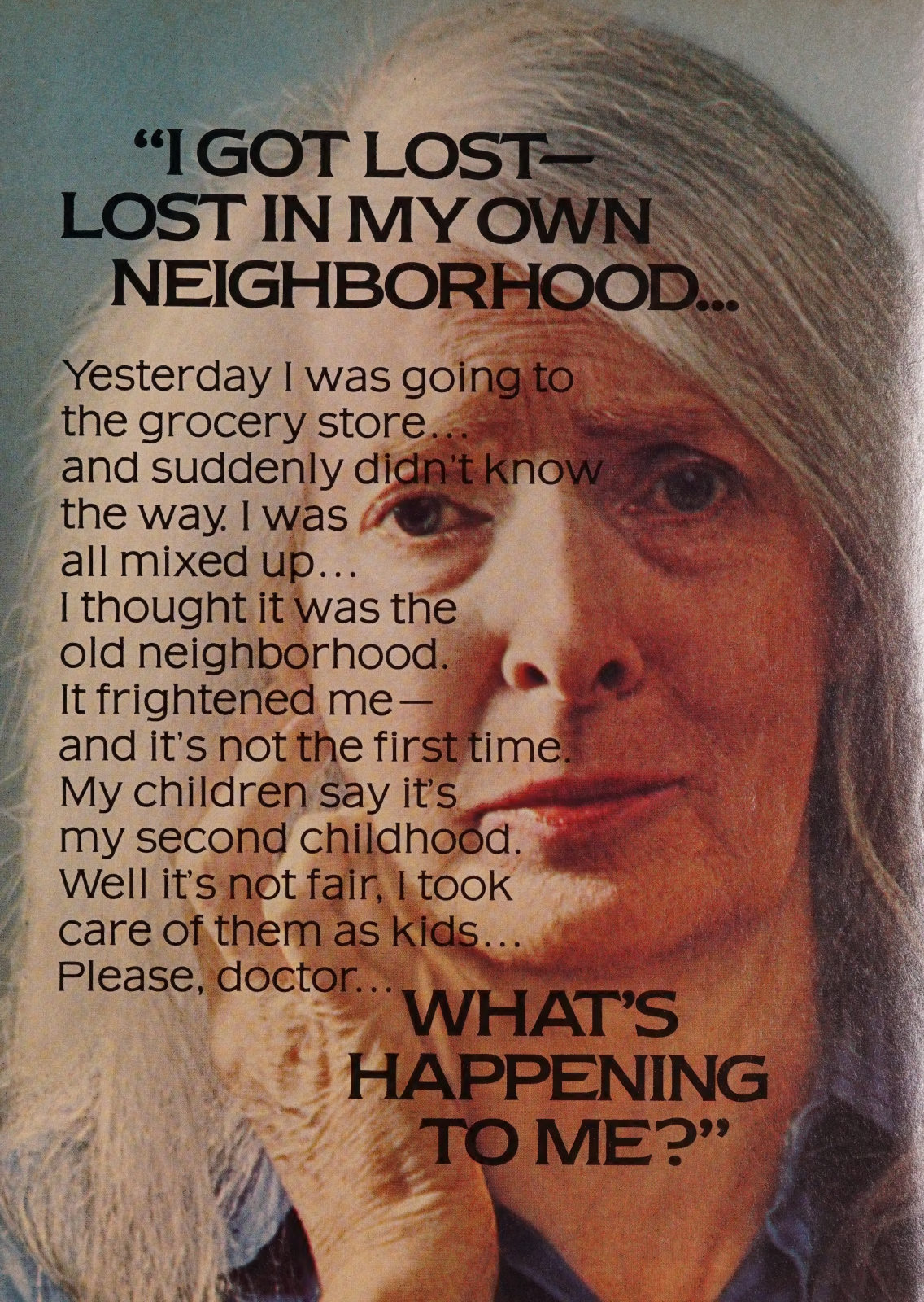

Larry Kramer, Co-Founder

Sincerely Yours,


Mel Rosen, Exec. Director


Harry Diaz, Circus Coordinator

P.S. Can you imagine being in Madison Square Garden with 17,596 of your very closest friends:



“I GOT LOST— LOST IN MY OWN NEIGHBORHOOD...”

Yesterday I was going to
the grocery store...
and suddenly didn't know
the way. I was
all mixed up...

I thought it was the
old neighborhood.
It frightened me—
and it's not the first time.

My children say it's
my second childhood.
Well it's not fair, I took
care of them as kids...

Please, doctor...

WHAT'S HAPPENING TO ME?”

GI distress and depression

John J. Schwab, M.D.

The intertwining of gastrointestinal dysfunction and depression is not a new problem. Quite a long time ago Hippocrates in *The Aphorisms* wrote, "The bowel should be treated in melancholics." But the problem certainly is a growing one of special importance to the family physician. It is important because depression and gastrointestinal dysfunction are so symbolically and biochemically intertwined that they are difficult to diagnose differentially. But perhaps this article will help a little with the problem of recognition and treatment of this complex duo.

An ominous indication of increasing depressive illness is the rising suicide rate, particularly in the 15- to 24-year-old group,



Dr. Schwab is professor and chairman of the department of psychiatry and behavioral sciences at the University of Louisville School of Medicine. He was the principal investigator of the epidemiologic study "Evaluation of Mental Health Needs and Services in the Southeastern United States."

where it doubled in the last 25 years. Similarly, the suicide rate for non-whites is higher than at any time in our history. Years ago, our chances of being afflicted with depressive illness serious enough to provoke suicide would have been 1 in 10 or 12. Now it's closer to 1 in 8. What makes these figures alarming is that only 10% of those afflicted receive treatment. Such untreated depression creates a piling up of susceptible people who may react to frustration, disappointment, and stress with chronic or recurrent illness, if not with suicide.

GI tract—so vulnerable

Why is the gastrointestinal tract so vulnerable to depressive illness? Why the close association between GI dysfunction and depression? Probably because early mother-infant relationships center on the infant's mouth, his ability to be satisfied orally, to be nursed and, later, to be fed and to feed himself comfortably. Any distortion of this important, complex satisfaction can easily jar the delicate balance between food and comfort. These oral distortions may eventually lead to fad dieting, obesity, or even extreme dependency—a kind of unsatisfied, infantile crying-out. Similarly, at the other end of the GI tract, badly managed bowel training can cause great mischief, often leading to a lifetime of inappropriate bowel

function and focus, such as chronic diarrhea or constipation. Like it or not, and long before we have any say in the matter, the GI tract becomes the sounding board of the emotions; it becomes heavily invested with psychic energy, from the infant's nursing to the senior citizen's irregularity.

To further complicate matters, some evidence of a biochemical association between depression and gastrointestinal dysfunction exists. We now consider that metabolic abnormalities of the neurogenic amines are the physiologic mechanisms in depression and the cause of depression in some cases. Fluctuations in the cerebral levels of catecholamines can be produced by variations of their available precursors. The intake, absorption, and metabolism of these precursors are influenced by factors affecting GI activity, such as diet, drugs, changes in the intestinal flora, and functional and structural disorders.

Frequency of symptoms

Years ago, depressed patients would probably have suffered loss of appetite and constipation. Today's patient often tries to fill a sense of inner emptiness or loss by overeating. Or he may indulge in drug or alcohol abuse or the latest fad diet. He may try to keep his spirits and his mental activity up by too much coffee (causing diarrhea), or too many diet pills

is made by measuring intraocular pressure.

Temporal arteritis is caused by chronic granulomatous inflammation in the large vessel walls, with polymyalgia rheumatica occurring in about 20% to 40% of cases. Diagnosis is made from elevated sedimentation rate. Lupus erythematosus cells and antinuclear antibody are usually absent. Because the condition may result in loss of vision as a result of central retinal artery occlusion, arteritis is considered an emergency.

Temporal arteritis is characterized by a moderate-to-severe aching, non-throbbing headache. Its chronic, steady, unremitting quality is a striking characteristic. The headache usually responds to simple analgesics, but recurs when they wear off. The headache and arteritis respond to modest steroid doses.

Acute sinusitis produces a sharp, aching pain of moderate-to-severe intensity, with localized tenderness over the affected sinus, and purulent, possibly bloody, discharge from the nose. It often occurs in pollen season. (Migraine is often misdiagnosed as sinus headache.)

Tolosa-Hunt syndrome is caused by periostitis of the superior orbital fissure. Such patients experience a headache of moderate-to-severe intensity that is steady, aching, and like temporal arteritis, strikingly chronic. Analgesics relieve the pain, but it recurs as the blood level of the analgesic diminishes. Palsies of the third, fourth, and sixth cranial nerves are usual, but vision is usually spared. The differential diagnosis includes tumor, aneurysm, or diabetic cranial nerve palsy. The condition responds well to steroids. A therapeutic trial of steroids can aid diagnosis.

Other extracranial causes. Headache can result from otitis media, acute tonsillitis and pharyngitis, orbital cellulitis, and other superficial abscesses or cellulitis. Also, headache can occur as a result of orbital tumor, sinus tumors, and nasopharyngeal cancer. Of course, a fractured skull or injury to the facial bones can produce headache.

Of those headaches of uncertain anatomic location, the most notable are those caused by injury without fracture or by intoxication (carbon monoxide, organic solvent, heavy metal fumes). When a patient complains of a chronic steady headache that is worse during the week and improved on weekends, look for a toxic exposure.

Headache associated with metabolic causes, such as kidney, liver, or endocrine disease, has few distinguishing characteristics. It can be mild to moderate in

intensity, steady, and holocranial, and generally not too severe, unless it is associated with a condition that may lead to cerebral edema.

Summary

If despite thorough evaluation, a diagnosis of functional or organic headache is still uncertain, you might order skull x-ray studies, radionuclide brain scan, computerized tomography brain scan, and appropriate blood tests. If none of these clear the way for a certain diagnosis, and if the patient is stable, then follow-up evaluations at intervals of 2 to 4 weeks may eventually help distinguish functional from organic headache.

For further information, I refer you to *Headache and Other Head Pain*, Wolff, HG, 3rd edition revised by Dalessio, DJ, New York, Oxford University Press, 1972.

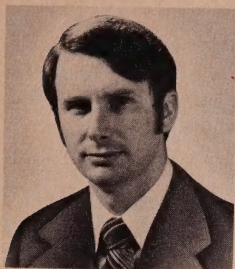


CONSULTANT invites readers to submit practical tips about diagnosis, treatment, equipment, and practice management. We will award an honorarium for each tip published.

Under the tongue

Nitroglycerin isn't the only drug that lends itself to sublingual administration. Many patients are grateful to know that morphine is rapidly absorbed under the tongue, as is atropine sulfate in hypodermic tablets. So, too, is buclizine hydrochloride and other soft tablets; they will work when the patient is too nauseated to swallow. For severe anaphylactic shock with marked hypotension, 0.3 ml of epinephrine hydrochloride solution injected under the tongue may be effective. This avoids the search for veins which may be collapsed, the dangers of intravenous epinephrine injection, and the relatively slower absorption from subcutaneous or intramuscular injections.

—**Ralph L. Gorrell, M.D.**
Sun City, Ariz.



Dr. Couch is assistant professor of neurology at the University of Kansas School of Medicine, Kansas City. He is a consultant in neurology at the Kansas City VA Hospital and is an investigator at the mental retardation research center at the University of Kansas Medical Center.

headache with exacerbation on Valsalva maneuver occurs.

Subdural hematomas occur in infants and the elderly, sometimes as a result of minimal injury. The headache is similar to that caused by epidural hematoma.

- Other increased intracranial pressure causes. Pseudotumor cerebri is an uncommon condition occurring most often in young women, possibly precipitated by tetracycline, birth control pills, excessive amounts of vitamin A or D, steroids, Cushing's disease, or hypoparathyroidism. Pseudotumor cerebri appears to be caused by low-grade cerebral edema, and produces the typical headache of increased intracranial pressure.

Malignant cerebral edema may follow head injury, and produces a headache the same as that of increased intracranial pressure headache.

Localized venous thrombosis may produce a mild-to-severe localized headache, usually with neurologic deficit. Generalized venous thrombosis or sinus thrombosis produces increased pressure with a typical intracranial pressure headache and obtundation or coma.

Hypertensive headache occurs with or without hypertensive encephalopathy. Headache with hypertensive encephalopathy is a syndrome of rapidly progressing hypertension with cerebral edema and increased intracranial pressure. Frequently, some obtundation, stupor, or coma accompanies it.

People with hypertension without encephalopathy who also suffer migraine find that high blood pressure frequently precipitates a cycle of migraine headaches that is relieved when the hypertension is treated. Patients with hypertension but

without migraine-type symptoms note a steady, aching, or throbbing pain that occurs whenever the blood pressure rises. Clearly, blood pressure evaluation is an important first step in the examination of any patient with headache.

Traction headache (due to intracranial hypotension with traction on the meninges) results from low cerebrospinal fluid pressure or from an inadequate amount of the fluid to support the brain. Traction occurs on the bridging vessels that cross the subarachnoid space. The traction headache is generally an aching, non-throbbing pain, either localized or holocranial, usually relieved by lying down and made worse by standing. The headache that follows pneumoencephalography or lumbar puncture is a traction-type headache.

Intracranial vascular headache is difficult to categorize. Various reports suggest that about 33% of patients with occlusive cerebrovascular disease have headache as a premonitory symptom or as a symptom accompanying transient ischemic attack or thrombotic stroke. In possibly 50% of these cases the headache was close to the thrombosed or stenosed artery. Aneurysms and arteriovenous malformations may give an intermittent, highly localized, moderately severe headache before rupture. Their characteristics are generally not distinctive enough to allow exact diagnosis before rupture.

Organic extracranial headache

Acute closed-angle glaucoma may cause excruciating pain in the affected eye with nausea and vomiting. But the more usual headache of glaucoma is steady and aching, occurring at night or in the early morning. Diagnosis

nausea, uncontrollable hiccups, and a slow pulse occur frequently in the increased intracranial pressure headache.

- Increased intracranial pressure causes: mass lesions. The mass lesion causing intracranial pressure headache may be a tumor or abscess, or it may be an intracerebral, epidural, or subdural hematoma.

Typically tumors run a subacute-to-chronic course, beginning with a minimal and nonspecific headache; as the tumor enlarges it causes progressively more intense intracranial pressure headache exacerbated by coughing or straining. At first, headache may be localized over the tumor, later becoming more generalized.

The headache of intracerebral hemorrhage is usually of sudden, intense onset, it may or may not be localized, and the patient may lapse quickly into coma.

Epidural hematomas usually occur in young adults. The classic course is head injury with unconsciousness, followed by a lucid interval, and then progressive coma. Local tenderness may appear over the hematoma; otherwise an aching, mild-to-severe

cles lasting weeks or months, with perhaps several headaches a day at the peak of the cycle. A small percentage of patients with cluster headache have Horner's syndrome, including miosis and ptosis, believed to be caused by intense vasoconstriction of the carotid artery with damage to the ascending sympathetic fibers in the arterial wall. Horner's syndrome may be transient or permanent.

Tension headache is thought to be caused by the chronic contraction of the occipitofrontal, temporal, or nuchal muscles and possibly from the buildup of metabolic waste products such as lactic acid. Tension headache is usually suboccipital, bandlike, or involves the whole head without gastrointestinal, visual, or other neurologic symptoms. It is of mild-to-moderate intensity. Usually both the onset and the end of the headache are gradual, and it lasts for hours (with one or more in a single day) or days.

Organic intracranial headache

Four major characteristics suggest organic headache: (1) recent changes in headache pattern, or the appearance of a new type of headache; (2) rapid increase in headache severity to unaccustomed proportions; (3) cough headache; and (4) abnormalities in the neurologic examination, especially if the headache is of recent onset. A further indication of possible organic headache is that the headache fails to fit the patterns for functional headaches.

Careful examination should reveal any neurologic abnormalities such as alteration of consciousness, personality change, cranial nerve palsies, spasticity, paresis, cortical sensory loss, ataxia, unilateral hyperreflexia, or a positive Babinski's sign,

all signs suggesting an organic lesion. Certainly neurologic abnormalities must be explained and correlated with the headache wherever possible.

Since the parenchyma of the brain is insensitive to pain, pain of intracranial origin comes from irritation or inflammation of the meninges, pressure on the meninges, or from similar processes affecting the pain-sensitive vascular structures. Sometimes pain is referred to specific areas of the head from affected intracranial structures. Headaches caused by intracranial structures fall into four major groups: inflammatory, increased intracranial pressure, traction, and vascular headaches.

Inflammatory headache is usually caused by acute meningitis (bacterial or aseptic), subarachnoid hemorrhage, or encephalitis. Meningitis and subarachnoid hemorrhage produce an intense headache with intense photophobia, developing rapidly (as in the case of subarachnoid headache) or over a period of several hours. The headache usually continues to increase in intensity until the patient becomes obtunded, or partially anesthetized, from the pain. Since the pain involves the entire head and the back of the neck, any movement of the head intensifies the pain. While the pain often initially responds to analgesics, it later becomes refractory. Stiff neck and positive Kernig's and Brudzinski's signs usually occur in alert patients, but not invariably; absence of these signs in obtunded patients does not rule out meningeal irritation.

Chronic meningitis caused by fungal infection or carcinomatous meningitis may produce a nonspecific low-grade, steady, aching headache. Stiff neck is

often absent, and slowly progressive obtundation and stupor may develop.

Brain abscess usually produces pressure headache similar to that of a tumor headache, but it may produce focal meningeal inflammation with subsequent headache.

Encephalitis usually produces a generalized, less intense headache of slower onset and longer duration. Obtundation is frequent and may obscure the headache. Stiff neck is absent, but a cough headache may exist if cerebral edema is present.

Increased intracranial pressure headache usually occurs late in the course of a mass lesion, after the mass has expanded enough to take up the potentially available intracranial space, including subarachnoid, ventricular, and venous sinus spaces. Such spaces can sustain some narrowing, allowing a mass lesion to expand initially without increased pressure. Eventually the closed rigid structure of the skull fails to accommodate the growth, pressure rises, and the headache ensues, accelerating rapidly to severe proportions.

The increased intracranial pressure headache is usually generalized and located bilaterally in the temples, suboccipital area, or vertex with possible neck muscle spasm. At first the pain is steady and aching, and analgesics may help. Later, when the pain becomes unbearable, narcotics are required. Local tenderness may develop over the mass lesion. Any type of maneuver that increases central venous pressure, such as coughing, straining, stooping, or bending over, causes a transient increase in intracranial pressure and a feeling that the top of the head is blowing off. Projectile vomiting, or sudden vomiting without prior

Diagnosing functional and organic headache

James R. Couch, M.D.

"Is it just a headache, Doctor, or is something really wrong?" How can you tell? This article thoroughly examines the major types of both headaches: functional and organic. Without a thorough understanding of both, a diagnosis of either is impossible.

Headaches are evaluated in terms of the following characteristics:

- prodrome
- type of onset
- location of pain
- type of pain
- duration of pain
- precipitating or intensifying factors
- factors that produce relief
- associated symptoms
- response to medication
- life history of headache
- neurologic or physical findings

Common functional headache

With functional headache the neurologic examination in most cases is normal, and diagnosis is made partly by exclusion.

Migraine headache, loosely

defined, is a nonorganic headache associated with nausea, vomiting, or diarrhea. It usually appears between the ages of 10 and 30, occurring 3 to 4 times more often in girls and women than in boys or men. Typically, migraine lasts from 6 to 24 hours, but rarely less than 2 hours. It may continue for several days, but seldom is there more than one episode a day. The intensity, type, and location (unilateral or bilateral) of pain are usually fairly stereotyped as are the photophobia, gastrointestinal, and visual symptoms.

The neurologic symptoms vary and seldom occur with every headache. Common features are photophobia, phonophobia, vascular instability with cool extremities, orthostatic changes in blood pressure, and a vasovagal type of syncope. Up to 50% of patients experiencing migraine also have blurred vision, teichopsia (fortification spectrum), or hemianopia. About 30% have accompanying transient neurologic symptoms, such as hemiparesis, hemi-sensory loss, or dysphasia at some time in their lives.

These migraine-associated neurologic symptoms are thought to occur because of focal cerebral ischemia related to vascular spasm with possible focal cerebral edema.

Patients with basilar artery migraine, thought to be caused by brain-stem ischemia following constriction of the basilar artery, may even lose consciousness. (It is important to distinguish this symptom of basilar artery migraine from loss of consciousness due to seizures.)

Cluster headache is usually an intense, unilateral, retro-orbital, or temporal headache with severe photophobia, tearing of the affected eye, and either a stuffy nose or a runny nose. Characteristically, the headache starts rapidly, lasts for 15 to 45 minutes, and dissipates rapidly. Most cluster headaches last less than 2 hours, although rarely they last 4 to 6 hours. Nausea and teichopsia are uncommon symptoms, and neurologic symptoms, of the type attributed to migraine headache almost never occur with cluster headaches.

Cluster headache occurs in cy-

When relief is needed...



them as a first choice if you think the patient will have difficulty avoiding the foods that react with them. Furthermore, unless you are very familiar with the pharmacology, do not use MAO inhibitors in combination with tricyclic antidepressants, since both drugs increase available amines in the brain and in the periphery. Serious side effects, principally hypertensive crises, may occur.

When to refer

1. Manic depressive illness. When detailed assessment reveals a past episode suggestive of hyperactivity, disorganization, and euphoria in the patient who is now melancholic, or if it reveals a family history of manic depressive illness, refer him to a psychiatrist or psychiatric center. If, after evaluation, the patient is given lithium carbonate, you can easily maintain him on this regimen in a general office practice. (Lithium carbonate is an extraordinarily specific treatment for manic depressive illness, including its acute melancholic episodes.)

2. Complex psychosocial problems. When detailed assessment reveals many complex interpersonal factors contributing to the melancholia, refer the patient to a psychiatrist or a psychiatric facility. Although detailed discussion of family problems or marital difficulties is best undertaken by such specialists, the general physician can gain a knowledge of counseling techniques if he has a particular interest in doing so and if he is willing to devote the necessary time.

Certainly if no improvement occurs in a month, and you have made an effort to intervene with supportive counseling, rehabilitative suggestions, and anti-

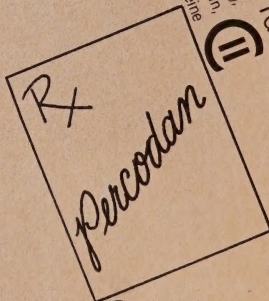
depressant drugs, then refer the patient to a psychiatrist. He may require hospitalization to remove him from a disabling environment or he may require shock treatments.

3. Suicide. Preoccupation with suicide must always be taken very seriously in any patient — the old adage that those who talk about it don't do it, is not correct. During the detailed examination always inquire about suicidal ideas. Questioning the patient will not pressure him into doing it; on the contrary, the patient will be reassured to know that the physician realizes this is a part of his melancholia (although a preoccupation with suicidal thoughts can also occur without depression). It is also important to inquire whether a method of suicide has been worked out, and then depending on the detail or lack of it, the physician is in a much better position to calculate how serious an intent the patient has. Be aware that men after age 50 suffering melancholia are in a particularly vulnerable age group, one that most successfully carries out suicidal ideas.

Young women have a high incidence of suicide attempts, but many of these attempts are impulsive gestures reflecting difficult psychosocial binds. However, gestures must be taken seriously because a miscalculated impulsive act has a chance of succeeding. Frequently, such attempts are made because the patient feels the physician is not truly interested; always be on guard for this development in young women.

In general, where preoccupation with suicide is a strong feature of melancholia, you should refer the patient to a psychiatrist for treatment and possible hospitalization.

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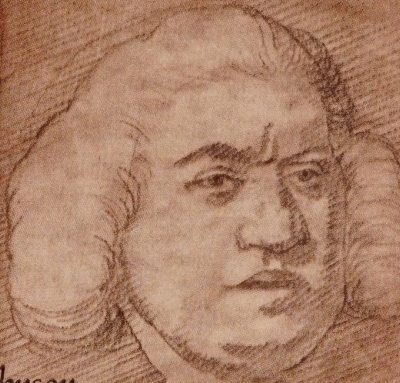
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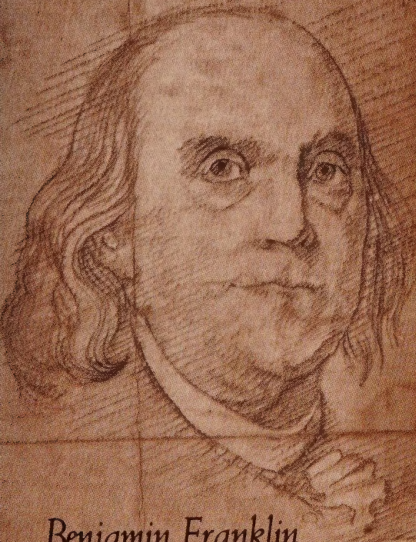
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Samuel Johnson



Benjamin Franklin



Isaac Newton



Charles Darwin

tion is essential (even for patients you know well). For instance, symptoms of depression can be the first warning sign of cancer. Endocrine disorders, particularly thyroid deficiency, adrenal insufficiency, and disturbances of calcium balance may also contribute to or be the major cause of the melancholia.

Consider using a symptom check list for the patient to fill in. Besides being a timesaver in a busy practice, it may provide the patient with an opportunity to reveal a problem that he is reluctant to tell you face-to-face. An example of such a check list, "The Zung self-rating depression scale," appears with this article.

Besides supplying an index to the severity of the patient's depression, the attention to detail on the check list makes it clear that you are concerned and sympathetic — the first major step to successful treatment.

Three factors

Three factors intertwine in melancholia: biologic, social, and psychologic. If you find profound biologic disturbances (such as loss of appetite and weight) and if social and sexual drives and intellectual concentration and decision-making abilities are impaired, the melancholia has usually advanced too far for psychotherapeutic intervention alone. An antidepressant given along with supportive counseling is more effective. Only after the patient feels better can he begin to benefit from psychotherapy and social rehabilitation.

If you do not find profound biologic disturbances, then antidepressants will be of little or no value and may only cloud the patient's consciousness, give him a dry mouth, and make him feel uncomfortable.

If social turmoil is a factor, try to determine whether it is acute or chronic. Certainly a sudden, overwhelming difficulty that has been encountered and resolved in the past offers far less of a problem than does a chronic difficulty.

Chronic situations represent a dovetailing of social and psychologic factors, often occurring as part of self-destructive or marginal coping mechanisms, such as excessive control of all the details in one's everyday life. Others manage their day-to-day environment adequately only through excessive dependence on major persons in their lives, or by manipulating life circumstances at great cost to their ever-declining energy reserves. Such persons usually require psychotherapy beyond the limits of what the general physician can provide in terms of both time and technique.

Even if the patient with chronic psychosocial turmoil does recover, expect further episodes to recur unless long-term psychotherapy and social rehabilitation intervene.

Drugs

1. Antidepressants. Antidepressants are the crucial adjunct to empathetic and supportive counseling. The major tricyclic antidepressants, which were introduced in the late 50s and which have changed little since then, are imipramine and nortriptyline.

Nortriptyline is slightly more sedating than imipramine. Yet in the early stages of depression, both drugs are useful as hypnotics, with a major portion given before bedtime, obviating the need for other hypnotics.

Demethylation of these compounds has led to the marketing of some tricyclic antidepressants

that are said to work faster than others, although no concrete evidence supports this. It is best to choose one or two of the tricyclics and stick to them, learning their potential as well as their side effects.

Prescribe 50 mg 3 times a day for persons of middle age and normal weight; anything below this is not therapeutic. You may try moving toward a maximum of 200 or even 250 mg a day. Reduce dosages for older patients, as is customary with most psychotropics. Because no evidence exists to show that tricyclics act prophylactically, withdraw them slowly after the melancholia has resolved.

If after 1 month the tricyclic drugs are still ineffective, it is unlikely that they will be effective. While an inadequate blood level could cause this, at the moment no reasonable, inexpensive measurement of circulating blood levels exists, so rather than increase the dosage, refer the patient to a psychiatrist.

2. Adjunctive endocrine treatment. Some evidence shows that in women a small dose of triiodothyronine (25 μ g in the morning for 2 weeks) potentiates the effects of tricyclic antidepressants. If you find a poor response to the tricyclics, you might try adding this.

3. Mild tranquilizing drugs. Frequently, depressive illness is accompanied by anxiety or agitation. In this case, add a mild tranquilizer such as diazepam or an equivalent, 5 mg 3 times a day. For more profound anxiety, try one of the phenothiazines, particularly thioridazine, 25 to 50 mg 3 times a day.

4. Monoamine oxidase inhibitors. Although MAO inhibitors are effective in some patients, they are more dangerous than tricyclic drugs. Do not consider

The Zung self-rating depression scale

Name _____
 Age _____ Sex _____ Date _____

	None OR a Little of the Time	Some of the Time	Good Part of the Time	Most OR All of the Time	
1. I feel down-hearted, blue and sad	1	2	3	4	4
2. Morning is when I feel the best *	4	3	2	1	3
3. I have crying spells or feel like it	1	2	3	4	3
4. I have trouble sleeping through the night	1	2	3	4	3
5. I eat as much as I used to *	4	3	2	1	2
6. I enjoy looking at, talking to and being with attractive women/men *	4	3	2	1	2
7. I notice that I am losing weight	1	2	3	4	2
8. I have trouble with constipation	1	2	3	4	1
9. My heart beats faster than usual	1	2	3	4	3
10. I get tired for no reason	1	2	3	4	3
11. My mind is as clear as it used to be *	4	3	2	1	2
12. I find it easy to do the things I used to do *	4	3	2	1	4
13. I am restless and can't keep still	1	2	3	4	3
14. I feel hopeful about the future *	4	3	2	1	3
15. I am more irritable than usual	1	2	3	4	3
16. I find it easy to make decisions *	4	3	2	1	3
17. I feel that I am useful and needed *	4	3	2	1	3
18. My life is pretty full *	4	3	2	1	3
19. I feel that others would be better off if I were dead	1	2	3	4	1
20. I still enjoy the things I used to do *	4	3	2	1	4

SDS Index 69 55 =

Although originally devised for psychiatric research, the self-rating depression scale (SDS) is extremely useful in family practice where most depression is first encountered. In less than 5 minutes a patient can be tested and scored, saving much needless probing and fruitless or repeated office visits. Comparative studies show that these measurements correlate reliably with more complex scales.

Although couched in common language, each question has been selected to represent a symptom of depression, either physiological (8 questions), psychological (10), or pervasive mood (2) symptoms. Half are converted from symptomatically positive to symptomatically negative questions to prevent the patient from anticipating the "right" answer. In addition, four multiple-choice answers instead of five keep the patient from selecting a middle-of-the-road, equivocal answer. Some questions may need brief discussion to help the patient select an answer representative of how he feels: for example, one who

is dieting and striving to eat less, might indicate in question 5 that his appetite is actually normal.

After the patient checks his answers, the physician slides the answer sheet under a clear plastic scoring key. On the key the answers to each question are numbered 1 through 4. Starred questions represent reverse symptomatology and are numbered 4 through 1. The number over each check mark is entered on the right-hand margin and totaled at the bottom of the sheet. The raw score is converted by means of a table: a raw score of 20 indicates an SDS index of 25; a raw score of 80 indicates an SDS index of 100. Higher scores indicate increased severity of depression. The mean index of depressed hospitalized patients is over 70, for example, and the normal control index is under 50. Above is a sample test with the plastic scoring card overlaid (in color).

©W. Zung, 1962, 1974. For further information, please contact: William W. K. Zung, M.D., Department of Psychiatry, Veterans Administration Hospital, Fulton Street and Erwin Road, Durham, NC 27705.

vious factors during routine history-taking, such as the death of a close relative or friend, but the family physician is in a position to detect more subtle yet equally potent stress, such as falling short of one's life goals.

If psychosocial stress occurs when the patient is having a biologic disturbance, chances of his developing melancholia are particularly high. For this reason melancholia occurs 4 times more often in women than in men: the menopause produces considerable endocrine turmoil, compromising the woman's physiologic capacity at a time when profound psychosocial changes are likely, such as the children leaving home. Many other biologic disturbances, such as influenza, serious injury, or thyroid deficiency may precipitate melancholia (Table 1).

Considerable evidence shows that some individuals are genetically disposed to melancholia. A greater than average family history of affective illness, suicide, and alcoholism, therefore, may indicate that this "biologic permission" is present. Uncovering this predisposition can help you. For example, for patients with possible manic-depressive illness, a knowledge of family history helps make the diagnosis and thus provides clues to the potential effectiveness of lithium.

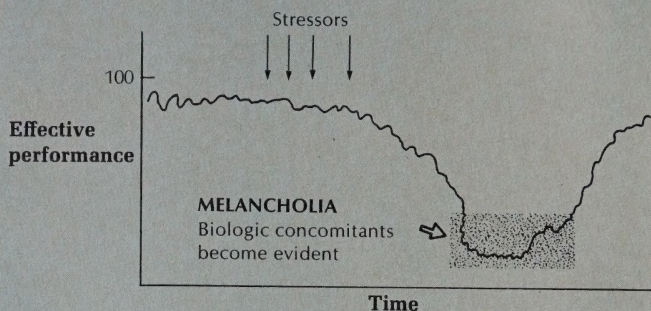
A detailed assessment

For optimum treatment first determine:

- What psychological, social, and biologic events are responsible for the distress
- How firmly established the biologic concomitants are
- How many signs and symptoms of depression the patient has (Table 2).

A detailed physical examina-

Table 1 — Schematic representation of melancholia



Once the biologic phase develops, melancholia becomes unresponsive to interpersonal processes. Although the illness is self-limiting, biologic treatments can shorten the course.

Table 2 — Signs and symptoms of depression

Mood

Sad, unhappy, blue, crying

Thought

Pessimism

Ideas of guilt

Self-denigration

} with rumination

Loss of interest and motivation

Decrease in efficiency and concentration (forgetfulness, indecisiveness)

Behavior and appearance

Neglect of personal appearance

Psychomotor retardation

Agitation

Somatic

Loss of appetite

Loss of weight

Constipation

Poor sleep

Aches and pains

Menstrual changes

Loss of libido

Anxiety features

Suicidal behavior

Preoccupying thoughts

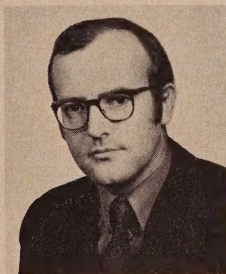
Threats

Attempts

Evaluating and treating severe depression

Peter C. Whybrow, M.D.

Five out of every 100 adults become significantly depressed at some time in their lives. Such people, baffled by behavioral and biologic changes including gastrointestinal disturbances, altered sleep patterns, difficulties in thinking and concentrating, and in social and sexual functioning often consult their family physicians rather than psychiatrists. Therefore, supporting and revitalizing the depressed patient becomes a management problem for the family physician.



Dr. Whybrow is professor and chairman of the department of psychiatry, Dartmouth Medical School and director of psychiatry at Dartmouth-Hitchcock Affiliated Hospitals, Hanover, New Hampshire. Dr. Whybrow has a Diploma of Psychological Medicine (Conjoint Board Psychiatry and Neurology) from England and is a fellow of the American Psychiatric Association.

Have you ever wondered why more people don't get depressed? For example, haven't you ever wondered why a wave of depression doesn't sweep across the nation each evening as most of us settle down to sample the world's latest tragedies on the evening news? Luckily, most of us have an innate capacity to maintain a healthy mental balance — most of the time — despite the vicissitudes of life. Although we are always in a state of flux, biochemically as well as psychologically, some kind of internal compass constantly swings about to keep us on a healthy course. This is usually an unconscious process, much like breathing, something we are not aware of until it becomes labored.

When depression does set in, it is evidence of an adaptive failure. I think of the severely depressed person as having lost something — the ability to cope successfully with his world — not as having acquired something.

Why "melancholia"?

Transient sadness and disillusionment are not severe depressive illness, although they may progress to it. To distinguish the two, I prefer to use the word

"depression" to describe the mood and to use the term "melancholia" to describe severe depressive illness. Melancholia, unlike transient depression, has a clear and precise natural history, like influenza, for example. Indeed, it can be very reassuring to explain to the patient that he has a self-limiting disease, particularly if he believes his disintegration is due to a lack of moral fiber!

Why it develops

Like all disease, the origins of melancholia are multiple, involving both biologic and psychosocial factors, particularly psychologic stress. We know that past experiences, especially of childhood and adolescence, determine what one finds disturbing or pleasurable. Thus, the individual's ability to cope with experience is related not only to his unique perception of the experience or stress, but it is also related to whether he has successfully adapted to a similar experience in the past.

Unless the physician has an intimate knowledge of his patient's life, precipitating stresses can remain obscure. Here the family physician has a distinct advantage over the specialist. The specialist may pick up ob-

offers the best chance for cure; that is, when the cancer is still a local disease. So far, information from the National Cancer Institute Screening Program points to a significant number of cancers that have been detected by mammography alone, many of them in patients under 45. In these patients, whose tumors were not palpable, the 5-year survival has been 95%! But does mammography increase the risk of cancer? We know that the average woman faces a 7% chance of developing breast cancer. The carcinogenic effect of x-ray exposure at current diagnostic levels is immeasurably small. Theoretically, a single mammographic examination raises the patient's risk of developing breast cancer from 7% to 7.07%.

The recent controversy over the benefit-risk ratio and the publicity that has been generated regarding possible "dangers of routine mammography" have prompted the American College of Radiology to suggest a policy regarding indications for mammography. In women with symptoms, mammography is an integral part of the evaluation. In women without symptoms, it is reasonable to perform a baseline mammogram between the ages of 40 and 50, and then at 1- to 3-year intervals, depending on the patient's vulnerability. Annual or other regular interval examinations are advised after the age of 50. Of course, every attempt should be made to keep x-ray exposure low by periodic monitoring of equipment and by keeping up with new developments in mammography. All women regardless of their age should be taught and encouraged to do frequent self-examination of their breasts as a supplement to the periodic professional examinations. 



Answers to 2-minute test

The questions (see page 46) are based on articles appearing in this issue of *CONSULTANT*. Answers reflect the opinions of the authors.

1. Renin measurements are necessary only for patients with low serum potassium and suspected primary aldosteronism. **Pyelography** is usually not necessary if a careful history, physical examination, and accurate urinalysis are done. Although a yearly chest **x-ray examination** is sound medical practice, it does not tell us more about heart size—and strain and coronary artery involvement—than the electrocardiogram.

see

Part 1—Selecting and evaluating the patient, from a three-part status report on hypertension

2. Statements one, three, and four are true. Diuretics consistently elevate renin. Propranolol exerts its major hypotensive effect through a central mechanism rather than by lowering renin.

3. One containing benzoyl peroxide. It may be less irritating than retinoic acid preparations and more effective than the older preparations.

see

Simple treatment for common acne

4. All of these

see

Diagnosing functional and organic headache

5. False. They should avoid laxative foods such as figs and prunes, but a high-fiber diet is a mainstay of therapy for all patients with irritable bowel syndrome, and in those with diarrhea fiber increases transit time.

see

Managing the irritable bowel: keep it from being an exercise in frustration

6. Diarrhea associated with irritable bowel syndrome is relieved with loperamide in nearly 100% of cases.

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Estradiol, the active estrogen at the cellular level

Estradiol is the primary estrogen of the human ovary—estrone and estriol are considered its oxygenated metabolites¹—and the major estrogen secreted during the reproductive life of the woman.²

Estradiol, not estrone, is the logical estrogen to replace

At menopause the normal cyclical production of estradiol declines, resulting for many women in the unpleasant symptoms of estrogen deficiency—hot flashes and atrophic vaginitis being the most common. ESTRACE provides the estradiol the ovary produced in the premenopausal years.

ESTRACE...the orally effective estradiol

Estradiol was long thought desirable in oral estrogen replacement therapy, but administration was not practical owing to erratic absorption. With the technique of micronization, dependable oral absorption has been demonstrated.^{3,4}

ESTRACE is rapidly absorbed, active at the cellular level, and follows the normal metabolic pathways in its utilization by the body. ESTRACE provides objective⁴ and clinical evidence³ of ready availability and biologic activity because estradiol can be assayed in plasma.

Easy to titrate to lowest effective dosage

ESTRACE is easy to titrate up or down as necessary for the individual patient to arrive at the lowest effective dose as soon as possible. Available in 1-mg. and 2-mg. *scored* tablets, ESTRACE is usually effective in a single dose of 2 mg. per day, administered on a cyclic basis.

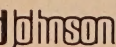
References: 1. Murad F, Gilman AG: Estrogens and progestins, in Goodman L, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co, 1975, p 1423.

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See following page for prescribing information.

Mead 
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ESTRACE[®]

(ESTRADIOL)

1-mg. and 2-mg. scored tablets

Estradiol...the only estrogen necessary in estrogen replacement therapy

Warning

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.^{1,3} This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.⁴ The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose.³ In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;³ it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equieffective doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY. The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.^{5,6} This risk has been estimated as not greater than 4 per 1000 exposures.⁷ Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, a type of epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.^{13,16} One case control study¹⁶ estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestagens are effective for these uses. If Estrace[®] is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus and the advisability of pregnancy continuation.

Clinical Pharmacology—17 β -Estradiol is the most potent physiologic estrogen and, in fact, is the major estrogenic hormone secreted by the human. Estradiol in Estrace[®] has been micronized and demonstrated to be rapidly and effectively absorbed from the gastrointestinal tract.¹⁷

Indications: Estrace[®] is indicated in the treatment of: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.) 2. Atrophic vaginitis. 3. Kraurosis vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. ESTRACE[®] HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

Contraindications: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients with progressing inoperable or radiation resistant disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

Warnings: There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast. However, women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be administered an estrogen with caution and a careful breast examination should be performed. A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens.¹⁸ An increased risk of post-surgery thromboembolic complications has been reported in users of oral contraceptives.^{19,20} If feasible, estrogen should be discontinued at least 4 weeks before, and not resumed until at least 4 weeks after, surgery of the type associated with an increased risk of thromboembolism. Estrogens should not be used in persons with thromboembolic disorders and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use or in patients with cerebral vascular or coronary artery disease. Benign hepatic adenoma should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypolemic shock. Hepato-cellular carcinoma has also been reported in women taking

estrogen-containing oral contraceptives.²¹ The relationship of this malignancy to these drugs is not known at this time. There is now evidence that elevated blood pressure occurs with use of estrogens in the menopause²² and blood pressure should be monitored with estrogen use, especially if high doses are used. Diabetic patients taking estrogens should be carefully observed for decrease in glucose tolerance. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

Precautions: A complete pretreatment and periodic physical examination should be given to estrogen users with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. Conditions which might be influenced by fluid retention such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Patients with a history of depression should be carefully observed. Preexisting uterine fibromyomata may increase in size while using estrogen. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be administered with caution in patients with impaired liver function. Estrogens should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. Estrogens should be used judiciously in young patients in whom bone growth is not complete. The following endocrine and liver function tests may be affected with larger doses of estrogen: a. Increased sulfobromophthalen retention; b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; c. increased norepinephrine-induced platelet aggregability; d. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T4 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered; e. Impaired glucose tolerance; f. Decreased pregnandiol excretion; g. Reduced response to metyrapone test; h. Reduced serum folate concentration; i. Increased serum triglyceride and phospholipid concentration. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Adverse Reactions: The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives: Breakthrough bleeding, spotting, change in menstrual flow; Dysmenorrhea; Premenstrual-like syndrome; Amenorrhea during and after treatment; Increase in size of uterine fibromyomata; Vaginal candidiasis; Change in cervical eversion and in degree of cervical secretion; Cystitis-like syndrome; Tenderness, enlargement, secretion of the breasts; Nausea, vomiting; Abdominal cramps, bloating; Cholestatic jaundice; Chloasma or melasma which may persist when drug is discontinued; Erythema multiforme; Erythema nodosum; Hemorrhagic eruption; Loss of scalp hair; Hirsutism; Steepening of corneal curvature; Intolerance to contact lenses; Headache, migraine, dizziness; Mental depression; Chorea; Increase or decrease in weight; Reduced carbohydrate tolerance; Aggravation of porphyria; Edema; Changes in libido.

Overdosage: Serious ill effects have not been reported following the ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration: 1. *Given cyclically for short term use only:* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (e.g., 3 weeks on and 1 week off). Attempts to discontinue or taper medication should be made at 3 to 6 month intervals. The usual initial dosage range is 1 or 2 mg. daily of micronized estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenance therapy should be determined by titration.

2. *Given cyclically:* Female hypogonadism; female castration; primary ovarian failure. Treatment is usually initiated with a dose of 1 or 2 mg. daily of micronized estradiol, adjusted as necessary to control presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

References: (1) Ziel HK, Finkel WD. *N Engl J Med* 293:1167, 1975; (2) Smith DC, et al: *N Engl J Med* 293:1164, 1975; (3) Mack TM, et al: *N Engl J Med* 294:1262, 1976; (4) Weiss NS, et al: *N Engl J Med* 294:1259, 1976; (5) Herbst AL, et al: *N Engl J Med* 294:878, 1976; (6) Greenwald P, et al: *N Engl J Med* 295:390, 1976; (7) Lanier A, et al: *Mayo Clin Proc* 48:793, 1973; (8) Herbst A, et al: *Obstet Gynecol* 40:287, 1972; (9) Herbst A, et al: *Am J Obstet Gynecol* 118:607, 1974; (10) Herbst A, et al: *N Engl J Med* 292:334, 1975; (11) Staff A, et al: *Obstet Gynecol* 43:118, 1974; (12) Sherman AI, et al: *Obstet Gynecol* 44:531, 1974; (13) Gal I, et al: *Nature* 216:83, 1967; (14) Levy EP, et al: *Lancet* 7:611, 1973; (15) Nora J, Nora A: *Lancet* 7:941, 1973; (16) Janerich DT, et al: *N Engl J Med* 297:697, 1974; (17) Yen SSC, et al: *J Clin Endocrinol Metab* 40:518, 1975; (18) Boston Collaborative Drug Surveillance Program: *N Engl J Med* 290:15, 1974; (19) Vessey MP, et al: *Br Med J* 3:1213, 1970; (20) Greene GR, Sartwell PE: *Am J Public Health* 62:680, 1972; (21) Mays ET, et al: *JAMA* 236:730, 1976; (22) Pfeffer RI, Van Den Noort S: *Am J Epidemiol* 103:445, 1976.

How Supplied: Estrace 1 mg; lavender scored tablets, NDC 0087-0755-01, bottles of 100. Estrace 2 mg; turquoise scored tablets, NDC 0087-0756-01, bottles of 100.

Full prescribing information is available in the Estrace physician package insert.

Mead Johnson
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arthrosis has no particularly associated extra-articular manifestations.

Soft-tissue rheumatisms.

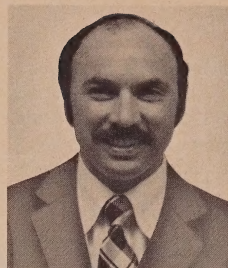
These conditions cause notably local areas of pain and tenderness with referred pain sometimes predominating. Common findings include the painful stiff shoulder from capsulitis, subacromial bursitis, bicipital and supraspinatus tendinitis, or a combination of these. Tennis elbow, with pinpoint tenderness over the lateral epicondyle of the humerus, may give rise to severe referred pain up and down the lateral aspect of the arm. Many areas on the posterior aspect of the torso and buttocks act as painful "trigger spots," probably reflecting minor degrees of subluxation, tearing, or inflammation in deeper and inaccessible perispinal ligaments and capsules. Trochanteric bursitis can similarly mimic arthritis, but reproduction of severe lateral thigh pain on pressure over the tender greater trochanter indicates bursitis. The soft-tissue syndromes are usually not associated with x-ray changes, except for occasional areas of ectopic calcification in previously torn tendons or capsules.

Chronic inflammatory arthropathies.

Rheumatoid arthritis nearly always affects the small joints of the limbs in a bilateral symmetric fashion, but may (and frequently does) affect many other joints, including the wrists, elbows, shoulders, upper cervical spine, temporomandibulars, hips, knees, and ankles. The symptoms of moderate to severe pain and early morning stiffness in some or all these joints should lead to a careful search for objective evidence of arthritis. The involvement of the

small hand joints and tendon sheaths may lead to prominent deformities, including swan-necking, a boutonniere posture, triggering, and ulnar deviation of the fingers. X-ray studies frequently reveal the classic changes of periarticular osteoporosis, uniform loss of joint space, marginal joint erosions, and subluxations in this widespread distribution, even when clinical signs are absent. Even before the rheumatoid arthritis is well established, other extra-articular manifestations of the disease may be apparent, including subcutaneous, tendon sheath or subperiosteal nodules; sicca syndrome with dry eyes and lack of saliva; and a high incidence of median nerve compression at the wrist, with overt or latent carpal tunnel syndrome. These relatively common and early extra-articular manifestations are important early clues to the underlying nature of the inflammatory arthropathy.

The rheumatoid variant disorders (seronegative spondylarthropathies) share many clinical features, with intra-group differences being largely manifest as the acuteness of the arthropathy and the predominance of the extra-articular features. Ankylosing spondylitis, sooner or later, always involves the sacroiliac joints and usually presents as low back pain, with or without a sciatica-like component. Pain and stiffness in the relative areas may suggest inflammation and fusion higher in the spine, including the thoracic and cervical regions. Large joint arthritis is quite common and may even precede symptomatic sacroiliitis. As in the axial skeleton, inflammation of shoulders, hips, and knees may quickly lead to a conspicuous loss of motion in the involved



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joints. Physical examination at an early stage frequently reveals local tenderness over one or both sacroiliac joints, restriction of lumbar and cervical spine motion, and limitation of chest expansion from fusion of the costovertebral joints. Up to 25% of patients have had recurrent acute iritis (the only major extra-articular feature of ankylosing spondylitis). The x-ray changes are variable, but are nevertheless virtually diagnostic. The sacroiliac inflammation leads to erosion of the cartilage with a pseudo widening of the joint, rapidly followed by dense subchondral sclerosis and later by bony fusion across the joint and periarticular osteoporosis. Any of these x-ray changes may precede or follow the symptoms and signs by months or years. Similar inflammatory changes lead to other characteristic x-ray signs that may be useful clues in early diagnosis. These include marginal syndesmophytes in the thoracolumbar region, anterior squaring of the thoracic vertebral bodies, and fusion of the cervical apophyseal joints.

The classic presentation of

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it's all
they get.**



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Reiter's syndrome is an abrupt onset of peripheral joint arthritis—often as a massively swollen (“sausage”) finger or toe—accompanied by conjunctivitis and urethritis in a sexually active young man. Additional early systemic features may include a characteristic rash (keratoderma blennorrhagica), a circinate balanitis, and superficial painless buccal or lingual ulceration. Remember, however, that in any individual patient this diagnostic triad may be incomplete; the arthritis can then dominate the illness. This often takes the form of a chronic hindfoot arthropathy with persistent synovitis of the ankle, subtalar or midtalar joints, together with periostitis beneath the calcaneum. The later radiographic signs of joint destruction and periarticular periostitis should suggest the true nature of the illness.

Psoriatic arthropathy may behave in a way similar to Reiter's syndrome, with an explosive synovitis of one of several small joints. More commonly, however, you see a sparse large joint arthritis or a uniform synovitis of the distal interphalangeal joints. As in ankylosing spondylitis, axial skeleton involvement may produce back pain and neck stiffness. The x-ray features may be similar to any of those already described, but uniform “pencil in cup” erosive destruction of several distal interphalangeal joints, or eventual fusion of a finger or toe joint is very suggestive of psoriatic joint disease. The x-ray distribution of those features then provides additional diagnostic clues. The detection of a psoriatic skin rash or nail pitting should alert you to the nature of the arthritis; however, the skin disease may be very limited in extent,

even arising after the arthritis has been established.

One of the more difficult diagnostic presentations of the seronegative spondylarthropathies is a “hot” joint (usually a “sausage” toe or finger) clinically indistinguishable from an acute crystal or septic arthritis. Unless you can confidently exclude acute crystal or septic arthritis clinically (unlikely unless the other features of the underlying seronegative disease are very evident), joint aspiration and microscopy are mandatory.

Synovitis. Acute crystal-induced synovitis (sodium urate gout) is usually a dramatically painful monoarthritis with an acutely swollen reddened joint, bursa, or tendon sheath. It most commonly involves the great toe in a middle-aged, obese, hypertensive man, and responds dramatically to colchicine. Acute gout can, however, affect other

“You cannot . . . be certain of an inflammatory arthritis unless you find visible or palpable synovial distention.”

areas and may be polyarticular in onset. Tophi or radiographic gouty erosions are not likely to occur in patients with acute gouty arthritis for the first time. Therefore, these patients should undergo joint aspiration and crystal identification when you first see them. A history of previous attacks, however, should lead to a search for punched-out erosions around the first metacarpophalangeal joint. Calcium pyrophosphate gout (pseudogout) most commonly affects the knees and wrists. The radiographic appearance of widespread chondrocalcinosis

(mainly in the fibrocartilages) is very characteristic of this metabolic disorder. I still recommend joint aspiration for definitive diagnosis, however.

Septic arthritis. Always consider this diagnosis in a patient presenting with an acutely inflamed single joint, bursa, or tendon sheath, especially a young person. If you suspect this disease, aspirate the synovial fluid for microscopy and culture. X-ray studies are rarely helpful in the beginning, but they may reveal reactive periostitis after several weeks. Many patients have fever and other obvious signs of systemic sepsis. Even so, synovial aspiration is mandatory, since the joint space may provide the first diagnostic proof of bacterial infection.

Collagen-vascular disease. When patients with systemic lupus erythematosus have polyarthritis, the physical diagnosis may be difficult. The inflammation is rarely severe, however, with arthralgias and episodic arthritis of the hands, wrists, elbows, and knees most noticeable. Rarely do x-ray changes occur, except in late-stage disease when a non-erosive deforming arthropathy of the hands occasionally occurs. Furthermore, other principal features of systemic lupus erythematosus nearly always soon emerge and achieve predominance. Thus, you should always consider lupus erythematosus in a young woman who has persistent or intermittent non-erosive arthritis, especially if her history reveals light-sensitive skin rash, pleuritic pain, or striking lymphadenopathy. Under such circumstances, the laboratory test for antinuclear antibody should be done.

WHEN VITAMIN DEFICIENCY IS PART OF THE PICTURE



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COMING IN

consultant

Polyuria and water intoxication: disorders of antidiuretic hormone

The differential diagnosis of diabetes insipidus, inappropriate ADH secretion, or psychogenic polydipsia can be difficult at best. Some of the intricacies of the causes and treatment of these challenging antidiuretic hormone disorders are clearly outlined by Dr. Edwin D. Bransome, Jr., endocrinologist from the Medical College of Georgia.

Common nail disorders: not always fungal

When you spot a nail abnormality, are you tempted to call it a fungal infection and treat it with antifungal preparations? Don't. First confirm the diagnosis. This article by Dr. Richard K. Scher offers suggestions for diagnosing and treating common nail disorders. Color slides of fungal and other nail abnormalities accompany the article.

10 questions physicians most often ask...

About treating pulmonary diseases

When to order blood gases; how to keep patients with asthma out of crisis; how to manage IPPB therapy, chronic lung diseases, or intractable pneumonia; and when to operate for lung cancer are a few of the most frequently asked questions about pulmonary disease. Dr. Sanders T. Frank answers 10 such questions, emphasizing new and better techniques in the management of lung problems.

Plus much more in future issues of **consultant**

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CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.

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PRECAUTIONS: Administer with caution and adjust to the requirements of the individual patient. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.

Patients should be cautioned to adhere to dilution instructions.

ADVERSE REACTIONS: Potassium intoxication indicated by listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac depression, arrhythmias, arrest and heart block. Vomiting, nausea, abdominal discomfort and diarrhea may occur.

OVERDOSAGE: In case of excessive use resulting in hyperkalemia or potassium intoxication, discontinue potassium chloride administration or take other steps to lower serum levels if indicated.

Cooper Compliance Tip

Help assure that your older patients take medications properly by printing your instructions in large letters. You might also send a copy of the instructions to the patient's spouse. Please forward your compliance tip to Cooper Laboratories, 300 Fairfield Road, Wayne, N.J. 07470, Att: W.F. Cronin.

Early detection of stress ulcers

John L. Sawyers, M.D.

Unless all seriously ill and injured patients are examined by routine, periodic gastroscopy, many stress ulcers and gastric erosions will go undetected. Studies show that within hours after injury (unrelated to ulcers), gastroscopy reveals superficial erosions in every patient. While it is true that most of these lesions are superficial, asymptomatic, and heal rapidly, it is also true that massive hemorrhage can result. Early recognition and management may save your patient's life. When you find stress ulcers how should you treat them? First, let's see how they begin.

Why and how ulcers begin

The causes of stress ulcers are varied: lesions of the brain or central nervous system, severe burns, major surgery or serious injury, sepsis, anoxia, steroid therapy, and certain ulcerogenic drugs such as aspirin, phenylbutazone, and indomethacin. Patients with one of these problems should be routinely examined for ulcers—and given prophylactic treatment.

Ulcers develop for a variety of reasons besides gastric hyperacidity, which is seldom men-

tioned today except in Cushing's ulcers. Cushing's ulcers develop after head injury, intracranial operations, or brain tumors, and form a distinct group of stress ulcers. These ulcers are more likely to be accompanied by full-thickness dissolution of the gastric or duodenal wall and to result in perforation. These ulcers are due to an oversecretion of gastric acid, as opposed to diminished acid secretion in patients with stress ulcers from other causes.

Alterations in the protective gastric mucus, or altered rates of gastric cell renewal, cause tissue breakdown. And shock markedly increases that susceptibility to tissue breakdown by producing a deficit in the metabolic energy of the gastric mucosa. Fasting produces a similar deficit, resulting in a subsequent reduction of available glucose substrate to the mucosa. Ischemia is probably the basic cause of stress ulcers, although some acid must be present for the first ischemic lesions to occur.

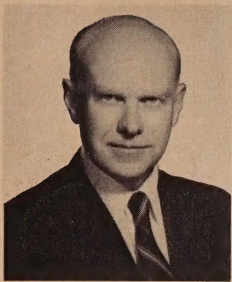
A back diffusion of hydrogen ion through the gastric mucosa may cause erosive gastritis. Exposure to bile salts may disrupt the gastric mucosal barrier; reflux of bile and pancreatic juice into the stomach is a frequent

complication of serious injury. Tests on rats and dogs receiving adrenocorticotrophic hormone (ACTH) show a reduction in the turnover rate of gastric mucosal cells. Perhaps increased circulating levels of ACTH after injury in man impair the healing ability of the gastric mucosal membrane. But whatever the combination of precipitating factors may involve, early detection and vigorous therapy for stress ulcers are essential.

Vigorous treatment

To reduce the frequency of stress ulcer bleeding use vigorous treatment for shock, and continuing antacid therapy; try to keep the gastric pH above 5. If massive gastrointestinal bleeding does develop, try to control the hemorrhage with iced saline gastric lavage. Give oxygen and control sepsis by draining any suspected abscesses. If replacement blood is needed, use the freshest blood available. Recently, for control of bleeding, perfusion of vasopressin through the celiac or left gastric artery has been effective, with reports of success in 35 patients. (The technique required a radiologist experienced in catheterization.)

Unfortunately, about 10% of patients with stress ulcer will



Dr. Sawyers is professor of surgery and vice chairman, department of surgery, Vanderbilt University, Nashville, Tennessee. He is visiting surgeon at Vanderbilt University and St. Thomas Hospitals. Dr. Sawyers is certified by the American Board of Surgery and the Board of Thoracic Surgery.

need surgery because of continuing hemorrhage. Considerable controversy exists regarding the choice of surgical procedure—no well-controlled comparative studies have been made. (Regardless of the choice of surgical procedure, too many patients die from the consequences of the condition that precipitated the stress ulcer.) The most frequently performed operations are: vagotomy-pyloroplasty; vagotomy-subtotal gastrectomy; and total gastrectomy. We prefer vagotomy in all patients.

In those short-stay patients who are reasonably good risks, use pyloroplasty and oversewing of the multiple bleeding points with truncal vagotomy. For those patients with more complicated problems who require a long hospital stay, do a 75% subtotal gastrectomy with vagotomy. Some physicians find rebleeding frequently follows vagotomy-pyloroplasty, but we find the rebleeding rate is 15%, and vagotomy-pyloroplasty procedure has the best survival rate—70%. If near total gastrectomy is desired, it is reassuring to note that, according to a recent report, death occurred in only 1 of 14 patients. 

AVAILABLE...

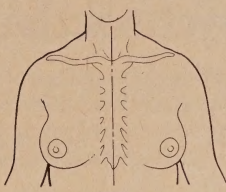
BREAST EXAMINATION RECORD

On this form, record the pertinent facts—positive and negative—of your patient's breast examination.

Breast Examination Record

Name _____ Age _____ Date _____

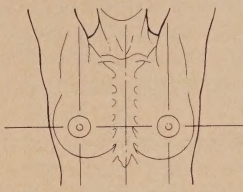
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ERECT



RIGHT AXILLA



SUPINE



LEFT AXILLA

On this sheet, record the pertinent facts—positive and negative—of the patient's breast examination. Attach the sheet to the patient's record.

Attach the handy form (actual size, 8½ x 11) to the patient's record. It graphically illustrates breast examination data for quick future reference.

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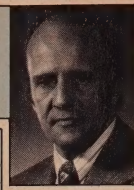
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MEDICAL DIRECTOR'S PAGE

Bruce H. Medd, M.D., Director of Professional Services



In our first communication in this series, we discussed the prudent use of psychoactive agents in light of the prescribing guidelines developed by the AMA Council on Mental Health and the AMA Department of Drugs. Your response to this article was so positive that we would like to explore this area further.

National patterns of psychoactive drug use

In the past few years, the prescription and use of psychoactive agents have been increasingly questioned. Arguments have been advanced that the United States is a uniquely over-medicated society, that permissive use of psychotherapeutic drugs bodes a weakening of traditional moral strength of character and that physicians are contributing to the problem through overprescribing.

A series of articles based on large-scale studies sponsored by the Psychopharmacology Research Branch of the National Institute of Mental Health (NIMH) has appeared in the medical literature from 1972 through the present.* These papers taken together provide a comprehensive basis for a rational evaluation of current patient usage and medical practices regarding psychoactive drugs versus alternatives such as nondrug use, alcohol and over-the-counter medications.

The general conclusions of these studies suggest that:

- use of psychoactive agents in the United States is neither unique nor atypical — in fact, the U.S. ranks fifth to seventh in usage amongst the 10 Western European countries surveyed
- physician prescribing habits are largely conservative — even cautious
- the American public has considerable reservations concerning the use of psychoactive medications
- use of these prescription agents may actually serve as alternatives to more harmful non-medical solutions to the problem of emotional distress

Recently, Dr. Leo Hollister put the issue in proper perspective when he wrote: "The proper use of psychotherapeutic drugs is not to be measured by how many people use them, or how often, but under what circumstances and with what effects. The prudent use of psychotherapeutic drugs demands the same skills required for the use of any other type of drug: proper diagnosis, proper selection of drug, proper doses and dosage schedules, and careful clinical follow-up. If these conditions are met, one need not worry about whether patients are getting too much or too few of these drugs."[†]

In the next few discussions in this series, we will examine in greater depth the areas of appropriate use within the framework of proper diagnosis, selection of drugs and follow-up procedures; also patient attitudes, knowledge and compliance problems.

*If you would like further information on the topic of Psychoactive Drug Utilization, just ask your Roche representative or write to me: Bruce H. Medd, M.D., Director of Professional Services, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

[†]Hollister LE: *JAMA* 234:942-947, Dec 1975

Sexual therapist: why not the family physician?

Domeena Renshaw, M.D.

Until 1966, medicine had little to teach about human sexual exchange. Now, very slowly, sex is being given curriculum time. It took 8 years at Loyola University of Chicago to get a 4-hour freshman class on human sexuality—for the previous 8 years the course had been an evening elective.

In other words, sex has been ignored—almost as though it were not a factor in the busy physician's practice. Yet more and more physicians suspect that sexual difficulties are behind the headaches, insomnia, and a host of other stubborn psychogenic ailments their patients bring to them. Many of your patients, too, may be hoping—perhaps only unconsciously—that you will pick up the clues and help. Many have no one else to turn to, or worse, they may seek help from charlatan sex therapists. Know it or not, like it or not, physicians are society's ideal sex therapists.

But, you may ask, how do I proceed? How do I ask that first probing, perhaps embarrassing, question? And what do I suggest for treatment? (I never took a course in this, remember?) Yet it is possible to probe, to listen,

to advise, and to treat—successfully.

The first problem is one of time. In a culture of speed and efficiency, plus high standards of service, physicians are time- and disease-oriented. How then will the average physician of today unlearn the "seven minutes, next patient, please . . ." routine developed through the years? Usually only through defeat. When we have done all the tests, asked for all the consultations, ordered another series of lower GI or sinus films, and Mr. Jones still complains of insomnia and abdominal cramps, or Mrs. Blake's headaches are worse with an analgesic—only then does a flashing light in our brain say, "Psychosomatic."

Take time to explore

Despite the pressure of time, we sit down and begin to probe. "How are things at home?" "Fine." "Family?" "Okay." "Any special worries?" "Well . . ." Now we are deliberately allowing time to bring the whole patient into focus. "Problems with the kids?" "Not really." "Is your husband well?" "Yes." "What about your sex life—any difficulty?" Here we may expect silence for a few minutes, and

we must learn to tolerate some silence. The patient is usually more tense than we are at this point. "Hard to talk about it?" Nod. Tissue. Silence. "What sort of sex problems are you having?" Now the patient will begin to share the distress possibly of years' duration. As physicians, we must be sensitive to how hard it is for this man or woman to bare these intimate feelings, yet how important and relieving it is to do it. The telephone buzzes, or the nurse knocks on the door. Twenty more patients this afternoon; how well you know it . . .

Mrs. Blake, 29, may be sobbing that she hates sex, has never experienced enjoyment, that she confronted her husband 3 months ago with years of faking climax. Two months ago, when her headaches got worse (and you ordered skull tomography), her husband told her he had another woman who doesn't need to pretend. Last week he threatened to move out. There are four children, all under seven; you delivered them all. Fine family. . . . How will you handle this family now? Or Mr. Jones, 38, who has a problem with premature ejaculation, says, "I love her. It's not her fault. I really try, but I just cannot hold

it back. I love my kids, Doctor." His wife has threatened to leave him. For both of these families, sex problems have become a severe family stress.

Sex problems as family stress. How many of you have come face-to-face with similar problems? How many of you make the time for needed discussion? It is hard to do this as a routine. In New Zealand, on a television program with me, a family physician said, "I pulled 8,000 cards—from the last 4 years—and found only one patient with a sex problem." In the limousine on the way back, he said, "Maybe it's because I just don't question about sex. . . . I don't have the time to get into it."

Treat both partners

However, there are timesaving alternatives when sex problems do emerge in practice. The most important first step is to let the patient know that the sexual problem does merit further discussion, and that both partners should eventually be involved. "Mrs. Blake, I am glad you had the courage to open up to me. It is most important, and I don't want us to be rushed for time. Here are two special sex history sheets—one for you, one for John. Fill them in separately and mail them back to me separately for confidentiality. Let me give you a half-hour appointment 2 weeks from now, so we can have some time to talk. If John doesn't want to come in, or if he has questions, let him call me."

The same approach can be made for Mr. Jones's premature ejaculation. For both of these commonly seen sexual symptoms, reassurance is in order. The outlook for symptom reversal is excellent if husband and wife cooperate as a couple. As a catalyst, the family physician can be

effective. As front-line psychiatrist and front-line sex therapist, family physicians can deal with 80% of presenting sex problems. Much of what sex therapy is about is educating and permitting patients to understand and discuss their own sexuality. The patients can do the rest themselves, because sex can be fun, and therefore success is self-reinforcing.

Nine practical suggestions

Consider these suggestions:

1. Timesaving sex educational aids are available (see resource list at end of article), or you can make them yourself. You (with your spouse's help) could tape a question-and-answer sequence of the most frequent sexual questions you encounter. A couple may listen to it alone and be encouraged to talk to each other about their sexual problems. This method saves you time and repetition. You could schedule a 15-minute interview afterwards for questions and clarification. You could make a tape on "Sex and Teens" which could be heard first by the parents, then by the teenager. You could make tapes on "Premature Ejaculation," "Woman's Orgasm," "Sex after a Coronary," "Sex after Hysterectomy," "Sex after Delivery," or whatever your practice needs may be.

2. A booklet of simple illustrations of sexual anatomy and physiology is useful to keep in your desk drawer, convenient for showing some basic structure (a great timesaver).

3. Illustrated booklets to help nonorgasmic women, and men with premature ejaculation and potency problems, are available. These sexually explicit booklets can be given to individuals, but preferably to couples, since the physician must be concerned

about dependent or seductive patients who have romantic dreams about seducing the "super" physician.

4. Instructional films or slides can be shown to a group by your assistant to conserve your time. Again, since the material is sexually explicit, have patients attend as couples, so there will be no misinterpretation of your motives.

5. A sex reading list for conservative couples is of value. It will guide them safely through the maze of sex manuals on the market, some of which may aggravate their problems rather than help (by setting up sensational or unattainable expectations), and some of which may have gross inaccuracies.

6. Set aside two evenings or two Saturdays a month to see a few couples. This is a critical factor, and one that will keep you from feeling pressured on a busy day.

7. Include your spouse as a co-therapist, if you can, to add the dual-sex dimension. It's more fun for you and also provides a partner for later discussion—often an illuminating experience.

8. Charge a realistic fee for your extra time, one that no couple will refuse. This makes it equitable for you.

9. Expect some anti-sex backlash from the community or your colleagues. Then you will not be unduly distressed when it happens. Share your couples' reading list with the critics—this may answer some of their questions and help educate the opposition.

What you will encounter

In medical practice, the most common nonorganic sexual dysfunctions are secondary or situational impotence, premature ejaculation, primary or secondary orgasmic dysfunction, and

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Indications / Dosage

• Duodenal Ulcer

Dosage: 300 mg. four times a day, with meals and at bedtime. Treatment periods should not exceed eight weeks.

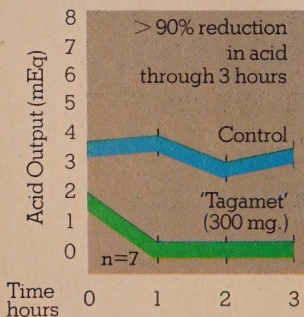
• Pathological Hypersecretory Disorders

Dosage: 300 mg. four times a day, with meals and at bedtime. In some patients it may be necessary to administer 'Tagamet' 300 mg. doses more frequently (not to exceed 2400 mg. per day) and continue as long as clinically indicated.

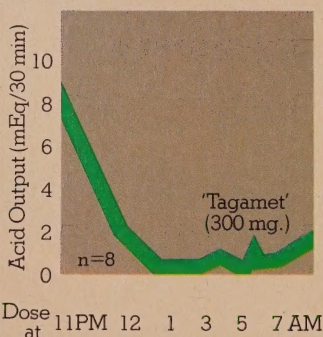
Concomitant antacids should be given as needed for relief of pain.

The 'Tagamet' Effect on Acid Secretion in Duodenal Ulcer Patients

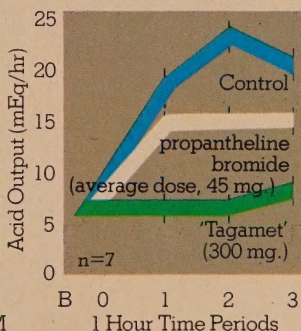
Basal Acid Suppression *



Nocturnal Acid Suppression *



Food-Stimulated Acid Suppression **



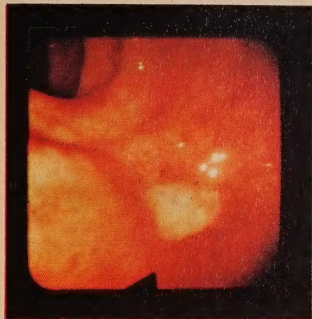
Please see last page for brief summary of prescribing information.

*Data on file, SK&F Medical Dept.

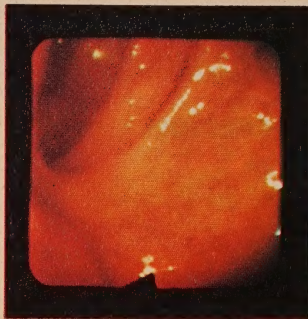
**New England Journal of Medicine, Aug. 21, 1975

Endoscopically proven Fast, complete ulcer healing

Endoscopic Examination of Duodenal Ulcer Patient on
'Tagamet' 300 mg. q.i.d.



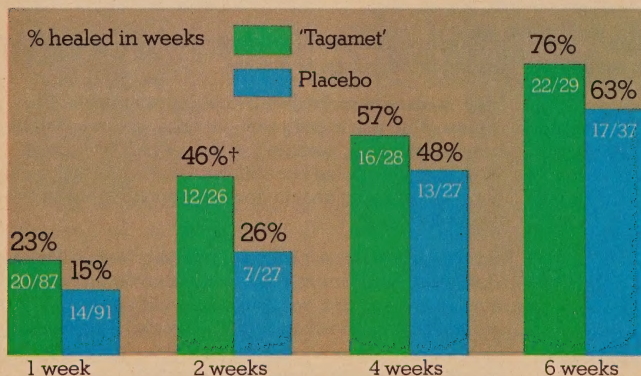
pretreatment



week 2

- In a U.S. double-blind study* of patients with endoscopically diagnosed duodenal ulcers, 'Tagamet' (300 mg. four times a day) significantly increased the rate of healing vs. placebo, proven endoscopically.

Heal Rates in Duodenal Ulcer Outpatients



Effective Symptom Relief

- In a U.S. double-blind study,* 'Tagamet' patients reported significantly fewer pain episodes and overall faster symptom improvement than placebo patients.

*Data on file, SK&F Medical Dept.

(all patients were permitted p.r.n. antacids for relief of pain)

†p<0.05

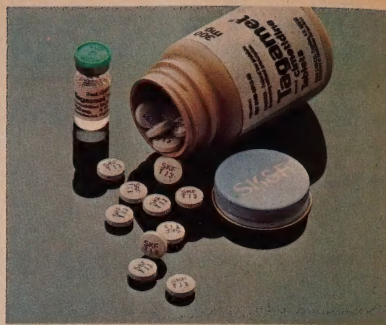
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- **Inhibits gastric acid secretion produced by all common stimulants:**
 - food, histamine, vagal, pentagastrin, caffeine
- **Promotes rapid ulcer healing**
- **Provides effective symptom relief**
- **Well tolerated**
 - based on clinical trials, the following are the most frequently reported adverse reactions:
diarrhea; dizziness; muscular pain; rash; mild gynecomastia

Before prescribing, see complete prescribing information in SK&F literature. The following is a brief summary.

Indications: 'Tagamet' (brand of cimetidine) is indicated in the short-term (up to 8 weeks) treatment of duodenal ulcer; and in the treatment of pathological hypersecretory disorders (i.e., Zollinger-Ellison syndrome, systemic mastocytosis and multiple endocrine adenomas). Concomitant antacids should be given as needed for relief of pain. Studies to date do not provide evidence of the safety of cimetidine in uncomplicated duodenal ulcer beyond 8 weeks.

Contraindications: There are no known contraindications to the use of 'Tagamet'.

Precautions: In a 24-month toxicity study in rats at dose levels approximating 9 to 56 times the recommended human dose, benign Leydig cell tumors were seen. These were common in both the treated and control groups, and the incidence became significantly higher only in the aged rats receiving 'Tagamet'. Reproduction

studies in animals have shown no evidence of impaired mating performance or fertility.

Lack of experience to date precludes recommending 'Tagamet' for use in pregnant patients, women of child-bearing potential, nursing mothers or children under 16 unless anticipated benefits outweigh potential risks; generally, nursing should be discontinued in patients taking the drug.

Adverse Reactions: Diarrhea, muscular pain, dizziness, rash, mild gynecomastia. A few cases of neutropenia have been reported, but no causal relationship could be established. Small, regularly observed, reversible increases in plasma creatinine and some increases in serum transaminase have been reported.

How Supplied: Pale Green Tablets: 300 mg. tablets in bottles of 100 and Single Unit Packages of 100 (intended for institutional use only).

Injection: 300 mg./2 ml. in single-dose vials in packages of 10.

Date of issuance Aug. 1977

loss of sexual desire in either sex. These usually respond to brief counseling.

A thorough physical examination, which must be done, usually reveals no urogenital or organic pathology. What then are the possible functional factors that need evaluating? Severe early sexual inhibitions; guilt because of religious orthodoxy, sexual identity confusion, persistent parental dominance, fear of venereal disease, pregnancy fears, fear of discovery, fears of homosexual tendencies, performance anxiety, resentment or anger, excessive alcohol, a clinical depression, various medications, deliberate control of sexual expression, or an unconscious dissociation of sexual feelings. Conflict and resentment, either long-standing or immediately before or during sexual overtures, may be anti-erotic, and may cause difficulties with arousal or performance in both partners. Details of paracoital exchange are important so that you can help unravel their conflict and suggest changes in destructive interactions.

Sexual blocks

Difficulty with sexual arousal is not a lack of something, but a symptom of some kind of block that needs discussion and resolution. Quite simply, perhaps simplistically, there are four A's and four D's to look for as blocks to the patient's enjoyment of sex:

Sexual blocks

A's	D's
Anxiety	Drugs
Anger	Depression
Alcohol	Deliberate control
Aging (if looked upon with anxiety)	Dissociation of sexual feelings

Knowledge of male-female physiology can provide you with

the understanding of why and how these blocks operate sexually. This basic medical knowledge, plus a thorough sex history, can give you the information you need to provide sex education and counseling.

Less common problems

There are many questions about sex waiting to be asked of you—by the teenager, by the pregnant woman, by the post-hysterectomy patient, by the diabetic patient, by the post-coronary patient, the hypertensive patient, the post-stroke victim, the alcoholic, and by those who have been injured surgically (such as the post-prostatectomy patient), or paraplegics. Today, for the first time, medical literature has provided more answers than ever before. Unasked and unclarified questions about sex breed unnecessary anxiety, misplaced anger, and even depression.

Sex is too often confined to coitus. Within their own value systems, there are natural alternative sexual expressions for both sexes of all ages, such as caressing, mutual masturbation, and oral sex. You must assume leadership by stating simply that the current stance of most theologians is one of situational ethics, a morality that examines individual circumstances rather than issues an archaic blanket condemnation. Each person will then have to make a moral choice about his and his partner's preferences. For too long we have mindlessly interpreted variations in sexual expression as sinful and perverted, when they are simply variants in much the same way that accents and dialects in language are variants. Here, perhaps, is the greatest contribution you can make to your community—to provide enlightened sex education for



Dr. Renshaw is professor of psychiatry and assistant chairman of the department of psychiatry at Loyola University of Chicago. She is also director of the sexual dysfunction clinic and the children's psychiatric outpatient program at the new Loyola Foster McGaw Hospital. Dr. Renshaw is a diplomate of the American Board of Psychiatry and Neurology.

interested clergy, so that the gap between church and science may be bridged—neither one rejecting the other, but each growing in the process.

Ideal sex therapist

In every culture, the "medicine man" has been the repository of ultimate intimacies. To whom does any person tell the size and shape of stool, the color and flow of menstrual blood, the force and feeling of urination? And we react with comfortable, professional interest. Now, with equally comfortable professionalism, the physician of the 1970s must be prepared to ask about early morning erections, duration of coital penetration, masturbatory activity, aversion or preference for oral or anal sex, details of early childhood sexual experiences, current patterns of sexual signals, and less common sexual practices. These facts are all as essential to a holistic medical history as are the details of contraception or of social stresses.

In no other area of medicine does the true meaning of "doctor," namely "teacher," show

such close application as in the field of sex therapy. It is here that persons with sexual problems have a need to know, to sort out their confusions, and to be taught accurate medical and scientific facts of human sexual exchange by those adequately trained and authorized to do so,

namely family physicians—the ideal sex therapists. By far, most sexual problems that arise in everyday practice are well within the range of effective intervention by concerned and interested family physicians. Are you ready and willing to accept the challenge?

Educational material about sex for the physician

1. Green R (ed): *Human Sexuality—A Health Practitioner's Text*. Baltimore, Williams & Wilkins Co, 1975.
2. Renshaw DC: Physicians and sex therapy. *South African Medical Journal* 50: 1092-1095, 1976.
3. Renshaw DC: Impotence in diabetics. *Diseases of the Nervous System* 36 (7): 369-371, 1975.
4. Renshaw DC: Sex problems of alcoholics. *Chicago Medicine* 78 (10): 433-436, 1975.
5. Renshaw DC: Sexual problems of stroke patients. *Medical Aspects of Human Sexuality* 9 (12): 68-74, 1975.
6. Renshaw DC: Emotional links to coronary disease — impact on sexual activity. *Practical Psychology for Physicians* 3 (3): 30-35, 1976.
7. Renshaw DC: Understanding masturbation. *The Journal of School Health* XLVI (2): 98-101, 1976.

Audiovisuals for physicians

1. One-hour audiocassettes. Spenco, Box 8113, Waco, TX 76706
"Coping with Sex Problems at Home," Domeena C. Renshaw, M.D.
"Sex Hazards in the Teenage Years," Domeena C. Renshaw, M.D.
2. "Yes Books of Sex." Multimedia, 1525 Franklin Street, San Francisco, CA 94109
You Can Last Longer
Masturbation Techniques for Women

Films

1. *Squeeze Technique*, 16 mm. Multimedia, 1525 Franklin Street, San Francisco, CA 94109
2. *Female Sexual Response*, 16mm. Focus International, 505 West End Avenue, New York, NY 10024

Books for patients

1. Bellevue F, Richter L: *Understanding Human Sexual Inadequacy*. New York, Bantam Books Inc, 1970.
2. *Our Bodies, Ourselves*: A book by and for women. The Boston Women's Health Collective, New York, Simon & Schuster, 1972.

Diabetic diet cards

A 24-hour Diabetic Diet (Adju

FOOD	PORTIONS	OUNCES	GR
Bread	3 lg. slices	3	
Orange	3 medium	15	48
3% or 6% Veg.	4 portions	20	60
Oatmeal, cooked	½ cup	4	1
Milk	1 cup	8	24
Egg	1 medium	1.7	
Meat	2 portions	5	
Butter	6 pats	1	
Soda Crackers	4	1	

Approximate Total Values:

1 kilogram (Kg.) = 2.2 lbs. A patient "at rest" requires
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Cards in packs of 25 are available at \$1 per pack, including postage and handling. To order use coupon.

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Please send me _____ diabetic diet cards @ \$1 per 25. Remittance enclosed.

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How to treat—and cure—vaginitis

Nine out of 10 women with vaginitis have Trichomonas, Candida, or Haemophilus infections. All these women expect prompt relief and should get it.

James H. Beaton, M.D.

Vaginitis has always been a therapeutic challenge; and the increased use of antibiotics and birth control pills, and sexual promiscuity have made it even more difficult to eradicate this problem.

Most patients expect prompt relief. If she fails to get it, a woman may go from physician to physician. It's not unusual for me to see in consultation a patient with a bagful of various creams, suppositories, and tablets. She has been to several physicians, tried the popular medicines, and still has her irritating discharge. Clearing up the patient's vaginitis is possible, but to do so requires an accurate diagnosis, an effective therapy, and clinical and microbiologic follow-up. The road to success begins with a thorough examination and good patient motivation.

What, why, and how

The patient wants to know *what* she has, *why* she has it, and *how* to get rid of it. You can't answer these questions until you have examined her and done microbiologic testing to confirm the diagnosis. You can make a clinical diagnosis, however, and gain

her confidence by explaining the nature of the infection. Here are some ways to do that:

Reassure the patient. Her vaginal discharge makes her feel uncomfortable and self-conscious. Explain that she has an infection, and that it will go away with proper therapy. I point out that vaginitis occurs in an environment that favors a persistent infection. The vagina is dark, wet, warm, and troublesome to treat. Menstrual blood provides an excellent culture medium for bacteria. Sexual intercourse can complicate the problem by irritating the vaginal mucosa and by serving as a source of reinfection. The endocervix and periurethral glands tend to harbor the infection.

Give specific instructions. I have had patients tell me that they were examined, given a tube of cream for the vaginitis, and ushered out of the physician's office without any instruction in using it! Specific instructions will help the patient avoid errors and omissions. For example, she must know whether to douche, and how and when to douche. Most women will sit on a toilet while douching—unless you tell them why this fails to cleanse the depth of the vagina.

A better douche can be achieved if the patient lies back in the tub with her thighs flexed about as much as they would be during a pelvic examination. Tell the patient that she should continue using vaginal medication during her menstrual period. Explain that the blood is a good culture medium for bacteria, and use as an example the fact that the itching of *Trichomonas* gets worse after a menstrual period.

Show the patient that you care. The physician's attitude can motivate the patient to follow the treatment. By organizing an effective program, you can show your interest and encourage her to cooperate. Your program will include diagnosis, therapy, and follow-up.

Making the diagnosis

Leukorrhea may be the only symptom of vaginitis, or the patient may complain of itching, odor, or painful intercourse. A vaginal discharge can be a symp-

Be sure to see the patient information sheet on douching that accompanies this article.

Patient Information

Date: _____

For (Patient's Name): _____

Ordinarily I do not advise douching. It is unnecessary for the healthy woman. I am advising you to douche, however, as part of the treatment program for your vaginitis. You will find it cleansing, comforting, and therapeutic.

I'd like you to douche before using the medication I've prescribed for you.

Here's how you should go about it:

- ☐ Add 1 tablespoon of _____ to 1 quart of warm water. This povidone-iodine solution is bactericidal and will help kill some of the bacteria causing your symptoms.
 - ☐ Use an ordinary fountain syringe with rubber tubing and nozzle.
 - ☐ Suspend the douche container 18 to 24 inches above the bathtub.
 - ☐ Lie flat in a bathtub. (Do not douche in a sitting position because the solution will not reach the upper vagina.)
 - ☐ Flex your knees and let them fall apart as you would for a pelvic examination.
 - ☐ Insert the nozzle into the vagina with a gentle rotating motion (2 to 4 inches or until the nozzle meets resistance).
 - ☐ Press the lips of the vagina with your fingers to keep the solution from flowing out.
 - ☐ Allow the solution to flow in until the vagina feels full. Hold the solution in for 15 to 20 seconds and allow it to gush out. Repeat the procedure until you use all the solution.
 - ☐ After douching, insert the medication I've prescribed.
- If you begin to notice any vaginal dryness or irritation after using this douche, please let me know.

I'll check on your condition in _____ weeks.

Please come in at _____ o'clock on _____.

Physician's Signature _____

tom of cervical cancer. Sometimes a complete workup reveals that the leukorrhea is physiologic and requires no treatment. When vaginitis is present, the cause in 9 out of 10 women is infection from *Trichomonas vaginalis*, *Candida albicans*, or *Haemophilus vaginalis*. Still another possible cause is gonorrhea.

- *Trichomonas* infections cause a watery, foul-smelling, yellow or greenish discharge. The fluid is often frothy. A source of reinfection is the patient's sex partner, who may harbor the organism in his urinary and genital tracts. To confirm the diagnosis, inspect a fresh wet specimen of vaginal fluid. Look for the pear-shaped protozoa *Trichomonas vaginalis*. The organisms are motile, and move with a characteristic wobbling and rotating motion.

- *Candida albicans*, or yeast infection, causes a white, cheesy discharge. The vulva may be extremely irritated, and the patient may have intense itching. Place a drop of the vaginal discharge on a slide, add a drop of 10% potassium hydroxide. Wait 2 minutes and examine the slide under the microscope for the pseudohy-

phae of *Candida*. Confirm the diagnosis by culturing the vaginal discharge on the chlamydospore agar of Nickerson and Mankowski. This can be done quickly and inexpensively in the office.

- *Haemophilus vaginalis* infections produce a milky discharge that may give off a sharp odor. Place a drop of the milky discharge on a slide and cover with a cover slip. Examine under high power for the typical clusters of small *Haemophilus vaginalis* bacteria. If you are doubtful, culture the fluid on Casman's medium to confirm the diagnosis.

- *Gonorrhea* may cause a purulent discharge. A Gram stain of the vaginal fluid may reveal gram-negative intracellular diplococci, indicating gonorrhea. You should have the discharge cultured on Thayer-Martin medium, for that is a good method to confirm the diagnosis.

Treatment

To be successful, therapy must be aimed at the cause of the vaginitis, and must be given for a long enough time to produce a cure. Here are the methods of treatment that have proved successful.

- *Trichomonas* infection responds to metronidazole, 250 mg orally 3 times a day for 10 days. The treatment should not be repeated in less than a month. In addition to systemic therapy, douching with a povidone-iodine solution every night will promptly relieve the itching and odor of *Trichomonas* infections.

The patient's sex partner should receive treatment during the same interval. For men, the dosage is 250 mg twice a day for 10 days. The man should wear a condom to prevent reinfection during coitus until both he and the patient are free of infection.

- *Candida albicans* infection responds to nystatin vaginal suppositories twice daily; the treatment should be continued for 4 weeks. Before she inserts the suppository, the patient should cleanse the vagina with povidone-iodine solution (1 tablespoon to a quart of warm water). The douche will improve the results of therapy because of its broad spectrum microbicidal effect in mixed infections. You must rule out predisposing causes of *Candida*. These include pregnancy, diabetes mellitus, antibiotic therapy, and oral contraceptives. Antibiotic therapy should be stopped if possible, and if the patient is taking birth control pills she should be switched to a combination product that has a low estrogen content.

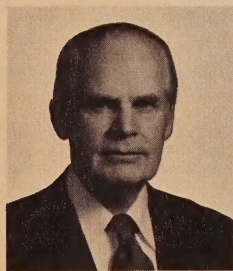
- *Haemophilus vaginalis* infection responds to triple sulfa cream or vaginal tablets. Have the patient insert a tablet or an applicatorful of the cream into her vagina twice a day for 4 weeks. Be sure to instruct the patient that she should use a povidone-iodine douche before inserting the medicine.

For patients who fail to respond to sulfa therapy, prescribe cephadrine or cephalexin (250 mg 4 times a day for 10 days). The patient's sex partner should also have this 10-day course of therapy.

- *Gonorrhea* can be treated by giving 2.4 million units of aqueous procaine penicillin G in each hip for a total dose of 4.8 million units. For the patient who is allergic to penicillin, you may prescribe tetracycline or spectinomycin.

Follow-up

Periodic pelvic checkups are necessary. They not only indicate whether treatment is work-



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THERAPEUTIC INDEX

ing, but they indicate to the patient your interest in obtaining a cure. The first two follow-up visits should be scheduled 2 and 4 weeks after the onset of therapy. At the time of the pelvic examination, repeat the microbiologic testing. Also scrub the vagina, cervix, and vulva thoroughly with an antimicrobial, such as full-strength povidone-iodine solution.

Give the patient a final examination about 4 weeks after the end of treatment. This checkup is essential to document a clinical and microbiologic cure. At this time, you can discuss with her the ways she can prevent reinfection, such as switching to an alternate method of birth control if the Pill contributed to her infection.

A comprehensive program

In research studies, resistant organisms have been shown to be a cause of treatment failure in about 5% of patients. Host susceptibility to infection is an equally important factor. Most uncured infections, however, represent a failure to make an accurate diagnosis and give the right treatment for a long enough period. A comprehensive program of the sequential use of a povidone-iodine douche, vaginal gel, and solution for a 4-week period generally achieves a high rate of cure in recalcitrant conditions.

One way a busy physician can still extend comprehensive care is by training an office aide to do most of this work under his supervision. An aide can become adept at preparing a wet suspension for him to examine, and at plating vaginal fluid on the various media. Moreover, the patients will appreciate her gentleness and availability for treatment on short notice.



Analgesics

Bayer Aspirin/Glenbrook	61
Darvocet-N 100/Lilly	164-165
Empracet W/Codeine No. 4/Burroughs Wellcome	2
Fiorinal/Sandoz	99
Magan/Warren-Teed	14-15
Percocet-5/Endo	22-23
Percodan/Endo	91, 152-153
Tylenol Extra-Strength/McNeil	122

Antacids

Dicarbosil/Arch	64
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Antiarthritics

Naprosyn/Syntex	144-146
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Antibacterials/Antiseptics

Macroclantin/Eaton	110-111
Septra, Septra DS/Burroughs Wellcome	38-40

Antibiotics

Achromycin V/Lederle	second cover
Ilosone/Dista	16-17
Tegopen/Bristol	100-101

Antidepressants/Tranquilizers

Etrafon/Schering	82-84
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Antidiabetic Agents

Diabinese/Pfizer	136-138
------------------	---------

Antidiarrheals

Imodium/Ortho	56-58
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Antiflatulants

Mylicon-80/Stuart Pharmaceuticals, Division of ICI	
United States Inc.	140

Antihistamines

Dimetapp Extentabs/Robins	142-143
Teldrin/Smith Kline & French	46

Anti-inflammatory Agents

Proctofoam, Proctofoam-HC/Reed & Carnrick	10-11
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Antimigraine Preparations

Cafergot P-B/Sandoz	fourth cover
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Antinauseants

Bendectin/Merrell	150-151
Dramamine/Searle	94

Antipruritics

Atarax/Roerig	4-5
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Antispasmodics/Anticholinergics

Bentyl/Merrell	108-109
----------------	---------

Ataractics

Librium/Roche	92-93
Miltown/Wallace	20
Valium/Roche	28-30

Bronchodilators

Brethine/Geigy	157-158
Elixophyllin/Cooper	53

Cardiovascular Preparations

Aldoril/Merck Sharp & Dohme	132-134
Arlidin/USV	42
Catapres/Boehringer-Ingelheim	32
Cyclospasmol/Ives	62
Inderal/Ayerst	114-118
Isordil/Ives	128
Nicobid/Armour (free Rx)	49-50

Contraceptives

Cu-7/Mark-7/Searle	18-19
Ovcon-50/Mead Johnson	6-8

Cough & Cold Preparations

Novafed/Dow	166, third cover
Robitussin-DM/Robins	21
Tussionex/Pennwalt	148-149

Decongestants/Expectorants

Chlor-Trimeton/Schering	72
Ornade/Smith Kline & French	86-87

Diuretics

Aldactazide/Searle	54-55
Dyazide/Smith Kline & French	12
Hygroton/USV	154-155

Educational Services

Institutional/Ayerst	44-45
Institutional/Roche	78

Electrolytes

Kay Ciel/Cooper	75
Klorvess/Dorsey	88-89

Geriatrics

Deapril-ST/Mead Johnson	102-104
Hydergine/Sandoz	34-36

H₂ Antagonist

Tagamet/Smith Kline & French	134 C
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Hormones

Estrace/Mead Johnson	68-70
----------------------	-------

Laxatives

Metamucil/Searle	81
Peri-Colace/Mead Johnson	67
Senokot/Purdue Frederick	106

Medical Equipment/Diagnostics

Littmann Stethoscope/3M Company	65
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Otic Preparations

Cortisporin Otic/Burroughs Wellcome	24
-------------------------------------	----

Parasympatholytic Agents

Bellergal-S/Dorsey	112-113
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Vitamins

Thera-Combex H-P/Parke-Davis	74
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Thyroid function tests: what to order and when

Joel I. Hamburger, M.D.

New tests of thyroid function make it possible to diagnose thyroid disease even when the patient has been taking iodides or medicines that change his level of thyroxine-binding globulin (TBG) (Box). The new tests are good ones, but they are new. To use the new tests efficiently, you need to understand what each test measures and what can

alter measurement levels. Let's begin with a brief review of thyroid function.

Thyroid secretory activity

In the first place, thyroid hormone is not one substance, but two: T_4 and T_3 . Most of the circulating thyroid hormone is bound to TBG. Less than 0.1% circulates in the unbound, or free, form. Thus, anything that changes the amount of the pa-

Abbreviations at a glance

T_4 = Levothyroxine

$T_4(D)$ = T_4 measured by the competitive protein-binding displacement radioassay

$T_4(RIA)$ = T_4 measured by radioimmunoassay

T_3 = Triiodothyronine

$T_3(RIA)$ = T_3 measured by radioimmunoassay

TBG = Thyroxine-binding globulin

TBG(S) = Thyroxine-binding globulin saturation (measured as the " T_3 resin uptake")

FTI = Free thyroxine index, obtained by multiplying the $T_4(D)$ times the TBG(S)

TRH = Thyrotropin-releasing hormone

TSH = Thyroid-stimulating hormone

TSH(RIA) = Thyroid-stimulating hormone measured by radioimmunoassay

RAI = Radioactive iodine uptake

T_3 suppression test = A trial of T_3 therapy when the RAI is elevated

T_3 stimulation test = A trial of TSH stimulation when the RAI is low

PBI = Protein-bound iodine

BEI = Butanol-extractable iodine

BMR = Basal metabolic rate

} Obsolete tests

tient's TBG can alter his level of T_4 or T_3 .

For example, estrogen therapy (such as birth control pills) and liver disease can cause the concentration of TBG to go up. Sometimes the patient's high level of TBG is hereditary. Androgen therapy, protein-wasting disease (such as nephrotic syndrome), liver disease, and heredity are among the causes of a lower than normal level of thyroxine-binding globulin. Phenytin and salicylates can displace thyroxine from TBG by competing for binding sites.

That so many things can change the amount of TBG is what made the protein-bound iodine (PBI) test and its modification, the butanol-extractable iodine (BEI) test, so prone to error. Like the basal metabolic rate (BMR) test, the PBI and the BEI are now obsolete. The free thyroxine index (FTI) has taken their place as the best screening test of thyroid function.

The free thyroxine index

The FTI is the best screening test for thyroid disease because it reflects the patient's serum level of active thyroid hormone (T_4). It is accurate even when the patient is on estrogens, androgens, or iodides. The normal FTI value is 1.5 to 4.2, but there are no units because the FTI is not a direct measurement of anything. It is simply an arbitrary numerical expression. You get it by multiplying the patient's serum T_4 by his thyroxine-binding globulin saturation, or TBG(S).

You can measure the patient's serum T_4 by a competitive protein-binding displacement radioassay. However, the radioimmunoassay (RIA) method is now preferred because it is more specific. The normal range for the T_4 (RIA) at the Northland

Thyroid Laboratory is 5.5 to 11.5 $\mu\text{g}\%$.

A simple method for estimating TBG(S) is the T_3 resin uptake. Bear in mind that the T_3 resin does not measure the serum T_3 . Radioactive T_3 is used in the assay, but the test reveals the saturation of thyroxine-binding globulin. For this reason, the T_3 resin uptake is now known as the TBG(S). The normal TBG(S) for most laboratories ranges between 25% and 35%.

Interpreting the FTI

Let's say the patient is in good health and his thyroid is working normally. Tests show that his T_4 (RIA) is 7 $\mu\text{g}\%$ —a normal value. The TBG(S) is 30%. Multiplying the two values gives a normal FTI of $7 \times .3$, or 2.1.

When both the T_4 (RIA) and the TBG(S) values are too high or too low, the patient has an abnormal thyroid. However, when one of the tests is high and the other is low, the patient probably has an alteration in his amount of carrier protein. A woman on estrogen therapy might have a T_4 of 12 $\mu\text{g}\%$, with a TBG(S) of 20%. Her free T_4 is high, and her thyroxine-binding globulin saturation is low. However, her FTI is $12 \times .2$, or 2.4—normal. A person taking androgens might have a T_4 of 4 $\mu\text{g}\%$ and a TBG(S) of 50%. The situation is just the reverse from that of a person taking estrogen. The T_4 is low, and the saturation of thyroxine-binding globulin is high. Yet the patient's FTI— $4 \times .5$, or 2—is normal. Thus, the FTI avoids the confusion which an abnormal value for either the T_4 (RIA) or the TBG(S) alone might cause.

The serum T_3 concentration

The FTI correlates well with the free T_4 concentration. Sometimes, though, you need to know

the T_3 level. Get a T_3 when you suspect T_3 toxicosis; two causes of it are multinodular goiter and an autonomously functioning thyroid adenoma. Other indications for measuring T_3 are after operation or ^{131}I treatment for hyperthyroidism, when Graves' disease is in its early stages, or when the patient could be producing excessive amounts of triiodothyronine to compensate for a failing production of levothyroxine. That situation can occur in Hashimoto's disease, degenerating goiter, or after operation or radioactive iodine treatment of the thyroid.

The best test of T_3 is the T_3 (RIA). This is an accurate way to detect compounds that are present in very small concentrations. The normal range at the Northland Thyroid Laboratory for the T_3 (RIA) is 60 to 190 ng%. Since an increase in T_3 (RIA) can mean either thyrotoxicosis or compensation by a functionally impaired thyroid, be sure to correlate a high T_3 with the history and physical findings.

The TSH(RIA) measurement

Another use of radioimmunoassay is to measure the level of thyroid-stimulating hormone (TSH) in the serum. The test is known as the TSH(RIA), and the normal value at Northland Thyroid Laboratory is less than 8 $\mu\text{U}/\text{ml}$.

Thyroid-stimulating hormone is produced by the pituitary and works through a negative feedback system to control thyroid function. In primary thyroid failure, the serum level of TSH goes up. Values between 8 and 15 $\mu\text{U}/\text{ml}$ are borderline; most patients with thyroid failure will have a TSH(RIA) level in excess of 30 to 50 $\mu\text{U}/\text{ml}$. Many patients with primary hypothyroidism will show a TSH elevation to 100

to 200 $\mu\text{U}/\text{ml}$. The magnitude of the elevation in TSH depends on the severity and duration of thyroid deficiency.

Another thing to remember is that not every patient with a high serum TSH will have clinical signs of hypothyroidism. A higher output of TSH (usually 20 to 30 $\mu\text{U}/\text{ml}$) may cause an impaired thyroid gland to make a normal amount of thyroid hormone. This can happen when the patient has Hashimoto's disease or simple thyroid enlargement from mild dysghormonogenesis. High TSH production may preserve the euthyroid state after a person has had a partial thyroidectomy or ^{131}I therapy.

A low TSH despite clinical signs of hypothyroidism suggests that the thyroid failure is secondary to pituitary failure. Still, you cannot diagnose hypopituitarism by measuring the TSH. Levels of the stimulating hormone are relatively low in both normal and hypopituitary persons.

Finally, you can use the TSH(RIA) to evaluate the response to thyroid therapy. As you treat hypothyroidism, the patient's TSH level should drop. The patient whose TSH remains high is not getting enough thyroid hormone. Conversely, a hypothyroid patient whose TSH level falls to 8 $\mu\text{U}/\text{ml}$ or less after treatment does not need a higher dosage of thyroid. Giving him more thyroid hormone is not necessary and could be hazardous.

Radioactive iodine uptake

The thyroid must remove iodide from the blood to make thyroid hormone. The 24-hour radioactive iodine uptake (RAI) gives an estimate of plasma clearance of iodide by the thyroid. A person with a normal thyroid will have a

RAI ranging from 10% to 15% up to 35% to 40%. However, a low uptake doesn't necessarily mean that the patient has hypothyroidism, nor does a high value always signal hyperthyroidism. In fact, the RAI is an indirect test. Its results can be influenced by drugs the patient is taking or by previous treatment with radioactive iodine or surgery.

Consider the case of a normal

man who is taking full doses of thyroid hormone. He is euthyroid, but his uptake of radioactive iodine will be low. Why? Because his thyroid gland has been put at physiologic rest by the thyroid therapy. It won't take up a "normal" amount of the radioactive iodine. In fact, a RAI uptake of more than 10% to 15% in the presence of thyroid therapy would indicate that the pa-

Table—Conditions to think of when the RAI is high, normal, or low

I. A high RAI can be seen in:

- A. Hyperthyroidism
- B. Euthyroidism
 - 1. Rebound after withdrawal of thyroid hormone or antithyroid drugs
 - 2. Recovery from subacute thyroiditis
 - 3. Early phases of Hashimoto's disease
 - 4. Compensated dysghormonogenesis
- C. Hypothyroidism
 - 1. Decompensated dysghormonogenesis
 - 2. Hashimoto's disease

II. A normal RAI can be seen in:

- A. Hyperthyroidism
 - 1. The patient is on antithyroid drugs.
 - 2. The patient has received iodides.
- B. Euthyroidism
- C. Hypothyroidism
 - 1. Hashimoto's disease
 - 2. After treatment for hyperthyroidism (^{131}I or surgery)
 - 3. Decompensated dysghormonogenesis
 - 4. Recovering subacute thyroiditis

III. A low RAI can be seen in:

- A. Hypothyroidism
- B. Euthyroidism
 - 1. The patient has taken iodides, thyroid hormone, or (less likely) antithyroid drugs.
 - 2. Hashimoto's disease
 - 3. Subsiding subacute thyroiditis
- C. Hyperthyroidism
 - 1. The RAI is low because the patient received iodides or antithyroid drugs.
 - 2. The patient is in the hyperthyroid phase of subacute thyroiditis.

tient has nonsuppressible thyroid function—a sign of potential hyperthyroidism.

A patient with dysghormonogenesis, by contrast, may show an elevated RAI but not have hyperthyroidism. His high uptake of radioactive iodine means that although his thyroid can trap a lot of iodide, it can't make thyroid hormone efficiently, and he may be hypothyroid. The Table lists the conditions to think of when the RAI is high, normal, or low.

The T₃ suppression test

A suppression test is a way of evaluating a high radioactive iodine uptake. The patient with the high RAI may have a gland that is compensating for iodine deficiency or dysghormonogenesis, or he may be in the rebound phase of recovery from subacute thyroiditis. Giving him 75 to 100 µg of T₃ a day for 4 to 7 days will suppress the high uptake of radioiodine. The usual fall in RAI is to less than half of the original value. A patient with dysghormonogenesis whose baseline RAI was 40% will show a drop in uptake to less than 20% after a week of T₃ therapy. Of course, an elevated RAI won't suppress if the patient has hyperthyroidism. Nor will T₃ lower the high RAI of certain other patients.

Someone with euthyroid Graves' disease, that is, an early stage in the disease before the development of the hyperthyroid features, may show a nonsuppressible rise in radioiodine uptake, and so may the patient with multinodular goiter or nontoxic autonomously functioning thyroid adenoma. T₃ therapy may not bring down the high RAI that can persist after hyperthyroidism has been treated with ¹³¹I or surgery. In other words, not every patient with a nonsup-

pressible elevation of RAI has hyperthyroidism.

Another caution about the T₃ suppression test concerns its possible hazards. Don't give T₃ to an elderly person with heart failure. The temporary rise in circulating thyroid hormone might cause cardiac decompensation. A very new test that will largely replace the T₃ suppression in the diagnosis of hyperthyroidism is the thyrotropin-releasing hormone (TRH) test. TRH is a hormone produced in the hypothalamus that stimulates release of TSH by the pituitary. TRH has been synthesized and is now commercially available. It has been shown that patients with nonsuppressible RAI values in

dary hypothyroidism. A patient with primary thyroid failure has a defective gland that won't improve no matter how much TSH he is given. Thus, his subnormal iodine uptake won't change after the TSH injections. The patient whose problem is pituitary failure will respond to TSH. His RAI will increase at least 10 percentage points after TSH administration, from a value of, say, 5% to at least 15%.

You can use the TSH test to confirm impaired thyroid function in a patient with goiter, Hashimoto's disease, or subacute thyroiditis. A normal person with a borderline low radioiodine uptake will show a rise in the uptake after receiving TSH.

"The normal FTI value is 1.5 to 4.2, but there are no units because the FTI is not a direct measurement of anything . . . You get it by multiplying the patient's serum T₄ by his thyroxine-binding globulin saturation."

response to T₃ also are pituitary nonresponsive to TRH.

The TRH test has important advantages over the T₃ suppression test: It can be done in one 20-minute visit and it is safer because no T₃ need be given. The TRH test cannot be used if the patient is taking full doses of thyroid hormone, for this will block the TRH response even in normal patients.

The TSH stimulation test

The patient whose RAI uptake is low can be stimulated with TSH to see if his gland will take up more radioiodine. An injection of 5 units of TSH is given daily for 3 days. A subsequent RAI can tell why the baseline reading was low.

The original purpose of the TSH stimulation test was to differentiate primary and second-

ary hypothyroidism. However, a person with impaired thyroid reserve—though clinically euthyroid—can't increase his uptake of RAI after an injection of TSH.

Another use for the TSH test is to see whether a person who is taking thyroid hormone actually needs it. A normal person who takes thyroid hormone will have a low RAI uptake. Giving him TSH will raise his uptake by more than 10 percentage points—suggesting that he does not need the thyroid. At the other extreme, the patient whose RAI goes up less than 10 percentage points after the TSH test probably does need his thyroid therapy.

A word of caution is necessary. Iodide ingestion can lower the uptake of RAI, and the value may not go up after an injection of TSH. For best results, stop the patient's iodide-containing drugs

for 2 or 3 weeks before giving him the TSH test.

The TRH test has partially replaced the TSH stimulation test, again because it is simpler and because you need not be concerned about incidental iodide ingestion. Patients with primary hypothyroidism as well as those with impaired thyroid function of milder degree will respond to TRH with a greater than normal release of TSH (that is, an increase over the baseline of 20 μ U/ml or greater). Normal patients respond with increments of 2 to 16 μ U/ml.

Things that alter the RAI

A patient who takes thyroid hormone or an iodide-containing medicine may have a low RAI uptake. The duration of suppression depends on the patient's thyroid function, the dosage of the medicine, and how long the patient has been taking it. Thyroid therapy will suppress the RAI of a normal patient, but the drug won't alter a thyrotoxic patient's high uptake of iodine. This is the basis of the T_3 suppression test. By contrast, the hypothyroid patient will have a low RAI whether or not he is taking thyroid hormone. Therefore, you need not stop the patient's thyroid hormone and wait for a certain number of days or weeks before doing the RAI uptake. A low RAI will exclude a diagnosis of hyperthyroidism, while a high RAI that hasn't been suppressed by thyroid therapy is strong evidence for thyrotoxicosis.

Ingestion of iodide can lower even the thyrotoxic patient's baseline RAI. However, his uptake of radioiodine will rise above normal after he has been off iodides for 2 or 3 weeks. Stop the obvious iodide-containing drugs such as saturated solution of potassium iodide and expect-

torants. Make sure, too, that the patient isn't getting his iodide in the form of kelp purchased at a "health food" store.

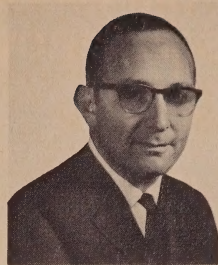
Things that alter the FTI

The free thyroxine index will show the thyroid function even when a patient has been taking iodides or has a drug- or disease-induced change in his level of TBG. However, treatment with thyroid hormone can affect the FTI. What happens to it depends on the dosage and type of thyroid therapy, and on whether the thyroid function can be suppressed.

Remember that circulating thyroid hormone normally contains about 4 times as much T_4 as T_3 . The level of T_3 is not reflected in the FTI, the T_4 displacement (D), T_4 (RIA), the PBI, or the BEI. This means that a patient given a pure T_3 compound will continue to have a low FTI even while receiving a toxic dose of T_3 . I see two or three such patients a year. The T_3 toxicosis has been induced by a physician who wanted to give enough T_3 to raise the patient's FTI to normal. It will not work! If anything, by inhibiting the production of T_4 , the T_3 therapy will cause the FTI to go down.

A note on thyroid therapy

We discourage the use of desiccated thyroid. The hormone content and the ratio of T_3 to T_4 are uncertain and inconsistent in desiccated thyroid, and so are the test values of the patient who takes it. If you do prescribe desiccated thyroid, don't follow the patient with PBIs. The PBI measures iodinated protein whether or not it contains active hormone. The danger of this is that the patient's need for thyroid replacement may be underestimated. I recall a girl who was



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receiving a combination of anti-thyroid drugs and 180 mg of desiccated thyroid a day for hyperthyroidism. She developed severe signs of hypothyroidism, but the clinical findings were dismissed by a pediatric endocrinologist because the girl's PBI was normal! Her T_4 (D) was exceedingly low, and the TSH(RIA) was greatly elevated. The patient was definitely hypothyroid, and needed a change in her therapy.

The newer mixtures of T_3 and T_4 were designed to produce test values that approximate normal. However, these new mixtures have no other advantage to justify their increased cost.

The preferred preparation is one containing pure levothyroxine. A proper dose will produce normal levels for the T_4 (RIA) and also for the T_3 (RIA). T_4 is broken down at the tissue level to triiodothyronine by monodeiodination. In the past it was thought that you had to give enough to produce an elevated serum T_4 concentration to correct hypothyroidism. It is now clear that this is not so. Actually we have been giving overdoses of T_4 . The hypothyroidism in most patients can be treated adequately with between 0.1 and 0.2 mg of T_4 daily.



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Catapres is an effective antihypertensive agent that seldom disturbs the sexual mechanism. Results of clinical trials¹ with Catapres indicate a low incidence of impotence and/or loss of libido. (Its most common side effects are dry mouth, drowsiness, and sedation,

which generally tend to diminish with continued use.)

Consider Catapres whenever a diuretic alone is not enough to lower blood pressure adequately. It adds an important measure of blood pressure control with little risk of impairing sexual function.

Please see the brief summary of the prescribing information on the last page of this advertisement for other potential adverse reactions as well as warnings and precautions.

ing CVP indicates that the right heart is probably overloaded. A PAWP that exceeds 18 mm Hg or rises rapidly usually indicates that the left heart may be overloaded.

- *Fever or excessive sweating* raises the fluid requirements. High fever may add 500 to 1500 ml a day to the insensible water losses. A patient who sweats ex-

cessively may lose another 500 to 3000 ml of fluid a day. Insensible water loss is considered to be water and sweat and is replaced with 0.3N saline (containing 50 mEq of sodium per liter of solution). Whenever iodinated contrast agents are used, their powerful osmotic diuretic effect must be considered. The dye used for an IVP can cause an osmotic diuresis of up to 7 ml of urine per ml of contrast agent used.

- *Gastrointestinal fluid losses.* Gastric contents are generally replaced volume for volume with 0.45N saline (75 mEq of NaCl per liter) with 20 mEq of KCl added to each liter of fluid. Remember, however, that the greater the acidity of the gastric juice, the lower its sodium concentration and the higher its chloride concentration. The pH of pancreatic secretions, by contrast, ranges from 8 to 8.9 because of the high bicarbonate content. Small-bowel fluid and bile have an electrolyte content similar to that of serum. Diarrhea fluid or fluid lost through an ileostomy may have a very high concentration of potassium. The patient with an inflammatory disease of the bowel may lose 45 or more mEq of potassium in each liter of

diarrhea fluid from an ileostomy or the colon.

- *Dehydration* can vary from slight to severe. Assume that a slightly dehydrated 70-kg man has lost fluid equivalent to at least 6% of his body weight, or a total of 4.2 liters of fluid. Moderate and severe dehydration represent 8% to 10% losses of body weight, respectively. These fluid

deficits should be replaced with saline or a balanced electrolyte solution such as Ringer's lactate. At least half of any fluid deficit should be replaced preoperatively if the patient needs emergency surgery.

Hyponatremia

Hyponatremia is usually dilutional, that is, the patient has taken in a relative excess of water. He may have replaced his perspiration by drinking water without enough salt, or he may have congestive heart failure, cirrhosis, acute renal failure, inappropriate secretion of ADH, or acute injury or sepsis. However, hyponatremia can also occur despite a normal or decreased total body water because of sodium loss from diarrhea, vomiting, adrenal insufficiency, or salt-wasting lesions. Hyponatremia from dilution by substances other than water can also occur occasionally. Such factitious hyponatremia may be caused by high concentrations of plasma lipids, or severe hyperglycemia. For each 100 mg/dl rise in blood glucose, the serum sodium goes down about 2 mEq/liter due to movement of water into the vascular compartment.

Fluid restriction is the usual treatment for dilutional hyponatremia. However, 3% saline can be given cautiously if the patient is symptomatic from the low sodium. Sodium deficits should be replaced according to the patient's hydration. Thus, for a patient who is normally hydrated or overhydrated, the sodium deficit can be calculated by assuming that the fluid space needing more sodium is equal to 20% of the body weight. For the moderately or severely dehydrated patient, the sodium deficit is best calculated by assuming that the water compartment needing more sodium is equal to 60% of the patient's body weight.

For example, let's say we have a 70-kg man who is moderately dehydrated from diarrhea and vomiting. His serum sodium concentration is 120 mEq/liter—compared to the normal value of 140 mEq/liter. Thus, his sodium deficit is 140 minus 120, or 20 mEq/liter. A fluid space equal to 60% of his body weight would contain 0.60×70 , or 42 liters. Thus, the total sodium deficit would be the 20 mEq deficit per liter multiplied by 42 liters, or 840 mEq of sodium. A liter of normal saline contains 155 mEq of sodium, so the patient's deficit could be replaced by infusing 5.4 liters of normal saline. However, a better way would be to replace half the deficit, then get another serum sodium and reassess the sodium deficiency.

Hypernatremia

Hypernatremia is usually due to a reduction in total body water. The best way to treat it is to give the patient water by mouth or give D-5-W.

Hypokalemia

Alkalosis can cause hypokalemia. For every 0.1 rise in pH, the

Don't put all your trust in the laboratory when a test result does not correlate with the patient's condition or with previous laboratory tests.

serum potassium falls by 0.5 mEq/liter.

A patient may lose potassium from diarrhea, diuretics, or steroid therapy. Severe hypokalemia may cause muscle weakness and adynamic ileus. The potassium-deficient patient may develop a metabolic alkalosis with an increased acid secretion in his urine (paradoxical aciduria).

Correct mild potassium deficiencies with oral KCl, but severe hypokalemia often requires I.V. infusion. Potassium is generally given intravenously in 50 ml of D-5-W containing 10 mEq of KCl infused over 1 hour. It usually takes 40 to 80 mEq of KCl to raise the serum potassium by 1 mEq/liter in acute cases.

Hyperkalemia

Oliguria, tissue breakdown, and excessive potassium intake can cause a high serum potassium. Treat moderate hyperkalemia (5 to 6 mEq/liter) by inducing a brisk diuresis. Treat more aggressively if the potassium is above 6, especially if the patient has peaked T waves and other electrocardiographic changes of hyperkalemia. Here are five ways to treat for life-threatening hyperkalemia:

1. *Give 10% calcium chloride.* An intravenous injection of 5 to 10 ml of calcium chloride over 5 to 10 minutes will help counteract the myocardial effect of potassium.

2. *Give sodium bicarbonate, 1 or 2 ampules I.V. over 10 to 20 minutes.* The alkalotic effect of sodium bicarbonate lowers serum potassium; the sodium opposes the effects of potassium.

3. *Infuse glucose and insulin* in a dosage of 50 ml of 50% G/W, or 250 ml of 10% G/W, containing 10 units of regular insulin over 10 to 20 minutes to 60 to 120 min-

utes, respectively. As the glucose enters the cells, it helps "pull" potassium in with it, reducing the blood levels of potassium.

4. *Give a cation exchange resin*, such as sodium polystyrene sulfonate. Order it by mouth or as a retention enema in a divided daily dosage totaling 40 to 80 gm.

5. *Resort to peritoneal dialysis or hemodialysis* if the patient has kidney failure and is not responding to the above measures.

Hypochloremia

The main cause of chloride deficiency is excessive removal of gastric contents by suction or vomiting. Treat this deficiency by giving chloride ion and by correcting any associated potassium deficit.

Calculate a chloride deficiency the same way you would a sodium deficiency. That is, for an adequately hydrated patient calculate the chloride deficit on the basis of a fluid space that is equal to about 20% of the body weight. If the patient is moderately or severely dehydrated, calculate the deficit on the basis of a fluid space that is equal to 60% of the body weight. Give one fourth of the chloride as potassium chloride; give the remaining three fourths as sodium chloride.

Hypocalcemia

About 40% to 50% of plasma calcium is protein bound, and about 45% to 50% is ionized. Complexed calcium, which is not ionized or bound to protein, accounts for the remaining 5% to 6% of the body's content of this mineral.

A low serum protein level is the most common cause of a low total calcium. Still, the patient will not generally suffer increased neuromuscular irritabil-

ity or tetany unless his ionized calcium fraction is low. Hypoparathyroidism tends to cause a fall in total and ionized calcium. However, massive transfusions or an alkalosis can lower the ionized calcium without causing the total calcium to drop.

If a patient has impaired cardiovascular function, which may be due to ionic hypercalcemia, give 10 ml of 10% calcium chloride over 10 to 20 minutes. During shock give 10 ml of 1% calcium chloride after every 2 to 4 units of blood.

Hypercalcemia

The patient with a high serum calcium may have an elevated serum protein (as in sarcoidosis), primary or secondary hyperparathyroidism, hyperthyroidism, hypervitaminosis D, or he may be showing the effects of immobilization. However, the most frequent cause of hypercalcemia is metastatic bone disease secondary to cancer of the breast, lung, or kidney.

Symptoms of hypercalcemia are weakness, lethargy, fatigue, confusion, and depression. The patient may have anorexia, nausea, and vomiting. Calcium makes the heart more sensitive to digitalis, and a high calcium may induce digitalis toxicity.

A very severe rise in calcium can cause stupor and coma, and treatment becomes a medical emergency. Here are some ways to treat hypercalcemia:

- *Infuse intravenous fluid rapidly.* This lowers the calcium by hemodilution, and promotes increased urinary loss of calcium.
- *Give diuretics* to increase the renal excretion of calcium.
- *Reduce the ionized calcium fraction* by giving sodium bicarbonate or hyperventilation to make the patient alkalotic.
- *Phosphate may be given intra-*

COMING IN

consultant

venously to combine with calcium, but this method of treatment is not usually necessary, and can be harmful.

• **Mithramycin therapy** can help if bone metastases caused the hypercalcemia. Steroids can lower the calcium by causing it to shift inside the cell. Calcitonin can also bring down the serum calcium.

Hypomagnesemia

Alcoholism with cirrhosis frequently causes a magnesium deficiency. Pancreatitis, excessive diuresis, and prolonged therapy with intravenous fluids are other causes. The symptoms resemble those of hypocalcemia. Look for hyperirritability of the central nervous system, flapping tremors, and coarse, jerking movements. Confusion and disorientation may also occur. In severe chronic alcoholism, a low magnesium may be associated with delirium tremens. Slightly low plasma levels may reflect much more severe deficiencies in tissue.

Treat severe hypomagnesemia by giving 4 to 6 gm of magnesium sulfate the first day, followed by 2 to 4 gm a day thereafter until the magnesium level is normal. Give the magnesium intramuscularly or slowly in the vein (1 gm of $MgSO_4$ equals 8 mEq of magnesium).

Hyperagnesemia

Body magnesium content can go up as a complication of kidney failure, particularly if the patient has taken magnesium-containing drugs such as milk of magnesia or magnesium and aluminum hydroxides. Increase the fluid intake to promote a diuresis, and order a diuretic if necessary. Prevention is usually possible by having the patient avoid drugs that contain magnesium. 

Narcolepsy: a major cause of excessive sleepiness

The patient who complains of falling asleep at dinner and behind the wheel may not be just overfed or overtired. He may be one of the 60% of sleepy people who suffer narcolepsy. In addition, he may suffer upper airway sleep apnea, an unusual and sometimes dangerous snoring pattern interspersed with moments of suspended respiration. To tell you about these and other sleep disorders is a group of four experts, including Dr. William C. Dement, from the Stanford University Sleep Disorders Center in California. Don't miss this article.

Measuring IgE: a help in the workup

Are you concerned about how to interpret IgE measurements? Are you ever in doubt about when to order skin testing and when to order the radioallergen sorbent test (RAST)? In this article Dr. Michael G. Perera begins with a discussion of IgE function in the blood serum. He then discusses some causes for high and low IgE levels and the overlap that often occurs between normal and abnormal values. You won't want to miss this clear, concise review.

Pleural fluid analysis: how to interpret the tests

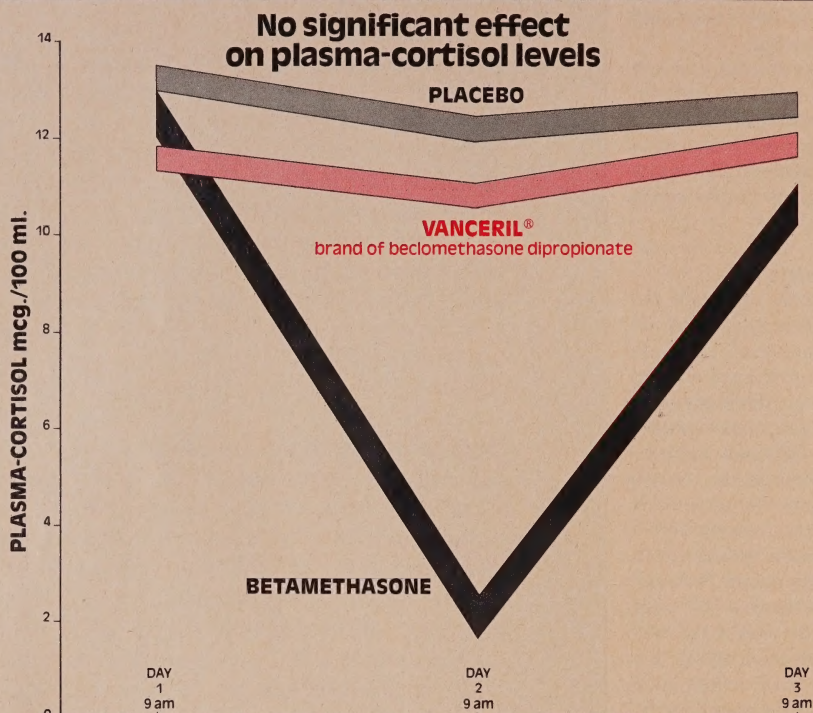
The number of diseases that give rise to pleural effusion can make diagnosis very difficult. Dr. Richard W. Light explains how an appreciation of pleural fluid motion dynamics and a logical step-by-step approach can make diagnosis less difficult.

Diagnosing acalculous gallbladder disease

Do you have difficulty determining when a patient has calculi in the biliary tract, no calculi, or genuine gallbladder disease? Do you have difficulty deciding when to do a cholecystectomy? And after the usual cholecystography, then what? To find out how to proceed with a step-by-step method for achieving a precise diagnosis and providing appropriate treatment, read this practical, illustrated article by Dr. Franz Goldstein. It may make your next decision—for or against cholecystectomy—easier.

Plus much more in future issues of **consultant**

Key to new successes



Plasma-cortisol levels at 9 a.m., during a two-day period, after oral administration of a placebo and 1 mg. each of betamethasone and VANCERIL (beclomethasone dipropionate) in normal male volunteers. Source: Files of Headquarters Medical Research Division, Schering Corporation.

A significant lowering of plasma-cortisol levels is accepted as evidence of suppression of normal adrenal function, such as occurs with systemically active steroids. In the experimental study results shown above, betamethasone exerted a marked suppressive effect on the plasma-cortisol level. By contrast,

VANCERIL (beclomethasone dipropionate) produced no suppression of the level. The absence of significant change in plasma-cortisol levels and concurrent freedom from adrenal suppression have been substantiated in numerous clinical studies of **VANCERIL** given in recommended therapeutic doses.

A major advance in steroid control of chronic asthma

Warnings

Particular care is needed in patients who are transferred from systemically active corticosteroids to **VANCERIL** Inhaler because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to aerosol beclomethasone dipropionate.

After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although **VANCERIL** Inhaler may provide control of asthmatic symptoms during these episodes, it does NOT provide the systemic steroid which is necessary for coping with these emergencies. During periods of stress or a severe asthmatic attack, patients who have been withdrawn

from systemic corticosteroids should be instructed to resume systemic steroids (in large doses) immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during periods of stress or a severe asthma attack. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning resting cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Please refer to the Clinical Considerations section for additional warnings, precautions, adverse reactions, dosage, and indications for use.

Removing swallowed foreign objects without surgery

Although we tell our children, "Never put anything into your mouth you don't want to end up in your stomach," they often do just that—particularly very young children. Frequently the object is one that is lying forgotten on the floor, such as a bobby pin or a nail or a loose carpet tack, and the child pops it into his mouth and swallows it. Here is a way you can remove such metal objects from the stomach or duodenum without resorting to surgery.

Use a small magnet—a pot-holder magnet is just the right

shape and strength for these elongated objects. Slip it into the end of a rubber nasogastric tube, leaving 1 cm projecting from the end, and pass the tube through the child's mouth into the stomach. With fluoroscopic control, the object can be picked up by the magnet and easily and quickly removed.

Dr. George M. Himadi and **Dr. Gary J. Fischer** of the department of diagnostic radiology, North Carolina Memorial Hospital, Chapel Hill, stress that although this technique is not new, it deserves renewed attention. So

far they have removed 16 assorted bobby pins, straight pins, and nails. They speculate, although they have not tried it as yet, that this same method could also be used to remove foreign objects from the trachea and the bronchi.

Be sure, advise the radiologists, to pass the tube through the mouth and not through the nose, lest the object disengage in the nose. And be sure to pretest the magnet's attractability to a similar object, if possible, because the iron content of nails, tacks, and pins varies. 



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Help patients cope with grief

Austin McCawley, M.D.

Grief is such an intensely personal and painful experience that the concept of trying to manage it may strike you as insensitive and mechanical. Nevertheless, you can learn to understand and accept the process of grief in your patients, and can take steps to help guide them through that process. Grief that has been accepted and worked through is not likely to harm the patient by delayed physical and psychological reactions. If you are aware of the patient's distress—even when it is disguised—you may be able to help him cope with this painful, disabling, and perhaps most truly human of all experiences.

Although much has been written about the management of grief, the subject can be reduced to three basic principles: do not abandon the bereaved, try to help the patient talk about his loss, and do not try to turn off his expression of grief. (Although the last two principles sound nearly the

same, the following anecdotes illustrate the difference.)

Three illustrations

Some years ago, when psychological and social services were less sophisticated than they are now, a young intern found himself deeply troubled by the death of a 10-year-old boy from cystic fibrosis. He had come to know the family, and he wished not only to help them through a time of painful grief but also, perhaps, to ease his own sense of failure. His chief resident advised him not to get involved—to drop the case—saying, "there is nothing more you can do."

The intern did not accept this advice; he kept in touch with the parents and tried to help them with their overwhelming grief. And he tried to help them overcome their unreasonable guilt over some of the treatment decisions that had been made with their consent during the last stages of their son's illness. Even though he referred them to a counseling service, he continued to hear

from them for several years. He was always surprised at the depth of their gratitude for what he considered simple kindness.

The advice to forget the family was not good medicine, and the intern had the professional conscience to realize it. However, the resident's warning was prompted by the knowledge that a physician must guard against getting overinvolved. Later in his career, the intern had to learn to keep some distance from his patients, for his sake as well as theirs. Yet the professional need to discipline and control one's emotional reactions does not call for the rejection of emotional upset in patients or their families. This family needed him not just for his medical skill, but also for his personal support—and he did not abandon them.

The second principle, helping the bereaved talk about his loss, is illustrated by the experience of a colleague in general practice. This physician had as a patient, a 30-year-old single woman whom he had been

treating for rheumatoid arthritis for several years. Since the death of her mother, 18 months earlier, her arthritis worsened and, more importantly, her personality changed. She was listless and tired, but not exactly depressed. She lost interest in her usual activities, and was irritable and critical of all her friends. She was in danger of losing her job because of her lack of energy and difficult behavior. Although she blamed the arthritis, the physician did not find it too severe.

The physician remembered that the patient had devotedly looked after her mother, yet seemed to have surprisingly little reaction to her death. Guided by sympathy rather than by design, he started talking about her mother, who had also been his patient. The daughter broke into tears, followed by anger, then despair. Before she left, she had regained control, but he knew he should see her again.

The second visit proved highly productive. The patient talked about the relationship with her mother and began to assess it realistically. She also began to look at her own personality which was of the self-sacrificing, offer-it-up type common in patients with rheumatoid arthritis. Both the physician and the patient felt a sense of relief that her long bottled-up feelings were finally coming out. He encouraged her to pursue her own interests and not take on everything people expected of her. As a result, her drive and energy returned, and although the arthritis continued to be a problem, it was a manageable one. This woman needed to go through a process of grief and its attendant guilt and anger to avoid the detri-

mental effects of denial on personality and physical health.

A third anecdote illustrates the benefits to the patient when the physician does not try to turn off grief. A surgeon received an office visit from the wife of a patient who had died from a pulmonary embolus following surgery. She consulted him about some vague physical complaints and then began to question him about her husband's death. She became angry, made several accusations, and then cried. The surgeon, embarrassed and afraid that the upset might be overheard in his waiting room, tried to defend himself. He could not get her to stop talking long enough to listen to any of his explanations; they were both talking at once, in rising tones. "You must try to get hold of yourself," he told her. This only made matters worse. Finally he decided to let her talk. She talked herself out, thanked him for listening, and then left the office. But before she left he made another appointment with her.

When he saw her next time, he found that she had accepted the sudden and tragic death of her husband and was handling the affairs of the family with dignity and courage. She was appreciative of his obvious concern and no longer blamed him for her husband's death.

Grief reactions

Erich Lindemann, in a pioneer work, studied the reactions of those who lost relatives or friends in the tragic Cocoanut Grove fire in Boston. He described characteristic psychology and physical manifestations of acute grief reaction: a very noticeable sighing respiration, especially when discuss-

ing their grief; lack of strength to the point of exhaustion; and digestive disturbances such as inability to eat, repugnance toward food, and abdominal discomfort. In addition, the bereaved feel detached and unreal, are tormented by guilt and self-recrimination, and are preoccupied with the deceased's image. They lack warmth in their relationships with others, reacting with irritation and anger. Restless and aimlessly active, they search for something to do, but lack the initiative to follow through. They find their daily routine meaningless and an effort. This constellation of grief reactions may appear immediately after the death, may be delayed or absent, or may be exaggerated. One or another aspect of the grief syndrome may become distorted.

The three stages of grief

Grief generally moves through three stages: an initial stage of numbness, a disorganization of feeling and behavior, and a stage of reorganization. Occasionally a person does not move beyond the initial stage, and mourning is delayed or postponed. The individual will often be one who has responsibilities for others and feels he cannot stop to grieve. He shows little or no reaction, and goes about his business as if nothing had happened. A subsequent stress or loss—even years later—may trigger a breakdown that is actually a re-enactment of the original, unexpressed grief.

Unexpressed grief can cause illnesses of all kinds. These include psychosomatic disturbances, hypochondriasis, conversion disorders and, in fact, most of the conditions listed in the psychiatric diagnostic

manual. The most common psychiatric reaction is, of course, the development of a clinical depression. Freud has revealed how feelings of ambivalence and hostility toward the deceased result in depression. Illnesses such as rheumatoid arthritis, ulcerative colitis, hyperthyroidism, and other conditions in which psychologic factors are known to play a role often follow the loss of a significant relationship. In a study of widowed men, the death rate during the 6 months after bereavement was 40% above the statistical rate for other men of the same age.

Some people show an emotional anesthesia that may persist for years, especially when loss is severe and sustained, as in the case of survivors of the concentration camps. This detachment may approach the level of schizophrenia.

Some patients behave in abnormal patterns including self-destructive kinds of acting out, such as promiscuity or addiction to drugs or alcohol. Patients may neglect their personal and business affairs, sometimes compulsively giving away their property to expiate guilt feelings. Most painful to the physician are patients who project their anger and accuse others of injustices or being responsible for the death. Occasionally, patients try to cope with their loss by identifying with and reproducing the physical symptoms of the deceased.

Overcoming the loss

The bereaved has to learn to live without the one he has lost, to relinquish the emotional ties and investments that have lost their meaning because they are now attached to a memory. He

also has to resolve whatever conflicts there were in the relationship and arrive at a comfortable attitude toward the memory of the deceased. He needs to release the emotions invested, and to express the pain of the loss. The importance of grieving is reflected in the many cultural rituals that encourage a communal sharing of grief. Grief is more intense in direct proportion to the degree of involvement with the deceased, whether positive or negative. Therefore, treatment should include examining and laying to rest resentments. Finally, the person has to re-adjust to a changed environment and go on to form new relationships—though that may take a long time. Engel has said that the clearest evidence that mourning is successfully completed is the ability to remember completely and realistically the pleasures and disappointments of the lost relationship.

Helping the bereaved

Ordinarily, the bereaved person does not turn to a physician for help, and when he does, he does not identify the problem as grief. He may not even mention the recent loss. Rather he may complain of depression, work difficulties, fatigue, anxiety, psychosomatic symptoms, or a vague discontent. When you are not consulted, but you see the need for intervention, you should take the initiative as tactfully as possible. The interview takes some skill—much more is involved than sympathetic listening.

As in any psychotherapy, your attitude, conveyed as much by nonverbal cues as by words, is crucial. Give the patient the time and the opportunity to approach the issue, knowing it

is a painful subject. Perhaps the first step might be a sympathetic comment about the death and a question about how the patient is managing. If the patient has difficulty responding, you can continue by expressing concern about his welfare, and mentioning anything he has observed that points to a problem. If this does not work, don't force the issue.

If the patient is completely blocked, he may have an underlying depression. However, do not assume a diagnosis of depression without confirmation—normal grief and clinical depression are difficult to distinguish except in the more obvious forms.

If you knew the deceased, you have a distinct advantage because the communication of shared experience establishes quick rapport. If you did not know the deceased, then taking a history and establishing facts not known to you may bring the emotions out during the interview.

If you are sensitive to the signs of unresolved conflict, you can reflect them back to the patient helping him to resolve any existing conflicts and to come to terms with the relationship. If you decide that the problem is important enough to warrant uncovering, proceed with care and tact. The aim is to identify and relieve the pressure, not to stir up troubled waters.

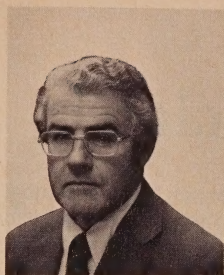
Even when a problem is obvious to others, the patient may not see it at all, and he may present a distorted picture. Do not challenge the distortion, but simply try to understand what really happened. The key is often in the significant details. By going over the everyday details of the patient's relation-

ship with the deceased, and by getting the patient to remember what really happened, you can help him recognize present feelings that are rooted in real experience. By recalling past feelings, the patient may accept them as being a part of himself. Of course, the extent to which the inquiry is pushed depends on the needs of the patient, his doubts, and how he feels.

Allow the patient to express guilt and restrain the impulse for quick reassurance. The bereaved may have done everything possible for the deceased and still blame himself for fancied mistakes and neglects and perhaps a few slips that he could not help. You can help him more by allowing that expression of guilt—looking at it for what it is—than by jumping in with remarks to the effect that he has nothing to blame himself for and he should stop worrying. If he could do that he would not be in your office. Such advice tells him to stop talking, in effect. Undoubtedly, many have already reassured him, with no success. So it is important to hear him out. Later, if he has enough help, he will arrive at that conclusion on his own.

If the patient has real cause for guilt, avoid assuming the role of judge, either by recriminating or forgiving the patient. Forgiveness is the more common error. Sometimes patients discover abruptly and overwhelmingly, in the physician's office, how badly they have behaved, and the revelation is more than they can handle. Try to help the patient find some solution he can live with. If the self-accusation goes on too long, you must set some limit and move the discussion in another direction.

You should accept the expres-



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sion of appropriate anger and reassure the patient. If the anger seems excessive, then you can try to understand where it comes from.

Some patients whose grief is especially agonizing fear they are going insane. Prompt reassurance helps, together with interpretations that tie the problems to the painful but human and normal experience of grief.

If you know the family, more often than not you are the best therapist. You can prescribe minor tranquilizers for anxiety and mild sedatives for sleeplessness, but sparingly and always in a secondary role. Tricyclic antidepressants are only indicated for clinical depression. Refer the more serious reactions and especially the severe depressions to a psychiatrist.

Last but not least, recognizing the role of loss and grief in precipitating or aggravating physical symptoms may make a considerable difference in the way you treat the patient's condition. Early, sensitive management of grief is truly preventive medicine.

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The team physician

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Before the season begins

Plan to attend all football games and to be on call for practice

sessions, supplying a substitute physician if necessary. Also plan to attend ice hockey, wrestling, lacrosse, and soccer games.

Plan to obviate possible misunderstandings or legal complications by putting in writing your important recommendations to school officials, coaches, and parents. In fact, check all aspects of legal liability with an attorney if possible.

See that the parents understand that you, while in your role as team physician, are not a personal family physician, and referral to the family physician is a parental responsibility.

Before the season begins, you need to review each participant's complete health record, investigating any positive findings that might have a bearing on athletic participation. You need to make it clear that, as undisputed authority for determining the mental and physical fitness of each participant, your medical opinion will not be subject to pressure from the trainer, athletic director, members of the coaching staff, school officials, or parents. For example, pressure to use local anesthetics to keep a player in a game must not be allowed; distribution of medica-

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Expanding the scope of the Pap test

John F. Seybolt, M.D.

Mention "Pap test" and invariably everyone thinks "cervical cancer detection" or "gynecology." This is not surprising in light of the wide publicity and educational campaigns given that application of diagnostic cytology. Nevertheless, the Pap test is adaptable to other organs and is useful for much more than cervical cytology testing. True, not everyone agrees that such applications of diagnostic cytology should be called "Pap tests," though there is ample justification for the name. The staining technique that bears Papanicolaou's name has become practically standard in most cytology laboratories. Such testing requires the microscopic examination of wet-fixed and stained exfoliated cells found in direct smears or sediments of secretions. Papanicolaou himself led the way in expanding the scope of this technique beyond gynecologic use.

Organ-adaptability

Organs with cavities or hollow components having access to the outside through direct openings or ducts, in other words, structures lined with epithelial tissues, lend themselves particularly well to cytologic examination. In such organs there is a constant exfoliation of cells—normal as well as pathologic—to the outside. This suggests that

cytologic tests can easily detect carcinomas, since a carcinoma is by definition epithelial. And such is the case. However, cytology studies can detect tumors other than carcinomas. If it can erode into an externally directed duct, or into a cavity reachable by an aspirating needle, any malignant tumor can theoretically shed cells that can be recovered for examination. Thus, sarcomas, lymphomas, and leukemias can also be included among the neoplasms whose presence may be detected through exfoliative cytology. Of course, by their site of origin, carcinomas are potentially diagnosable by this method at an earlier stage of growth when they are still non-invasive and too small to cast a shadow radiologically.

Until recently, non-gynecologic Pap tests received almost no publicity except in the research world, but they have been in constant use, worldwide, for many years. Unfortunately, they have not yet been found practical as a mass-screening device for the general public. Today these tests are almost exclusively done for the following special problems:

- The diagnostic workup of a patient in whom a malignant neoplasm is suspected
- The determination of the site of the primary lesion in a patient with signs of a malignant growth but in whom the tumor has not yet been localized

- The determination of the effect of treatment in known cancer
- The care of individuals at high risk for developing cancer, including workers in certain industries.

Urinary application growing

Recently, in our laboratory at least, the cytologic evaluation of urinary tract specimens has been growing faster than that of other non-genital types of specimens. We have analyzed about twice as many urine specimens as the next most frequently studied specimens—pulmonary specimens. Urine specimens consisted of voided, catheterized bladder, and ureteral urines. Urine voided after prostatic massage is also occasionally submitted when cancer of the prostate is suspected. Another indication for cytologic examination of the urine is unexplained hematuria, as is a filling defect in an intravenous or retrograde pyelogram.

Urinary cytology studies are most successful with urothelial tumors, especially bladder cancer. Even the early, non-invasive stages of such tumors can be detected cytologically. Occasionally, malignant-appearing cells have been found in urine samples many years before a tumor could be confirmed. Other tumors, including neoplasms of the renal parenchyma and of the prostate, are less likely to shed diagnostic cells into the urinary channels until a much later stage

of tumor development, so the early detection of such tumors by this method has been disappointing.

Urinary cytology is also useful for evaluating the results of tumor treatment and for detecting recurrence of tumor after treatment. For example, at our hospital, patients with vesical cancer who are given courses of thiotepa receive periodic cytologic study of urine specimens at certain intervals during and after treatment.

Urinary cytology also provides a convenient method for a long-term surveillance of certain industrial workers who are exposed to carcinogenic compounds (such as the aromatic amines, which are known to select the bladder as their target). In a 6-year study of 858 workers in five dyestuff factories, 17 employees developed tumors of the urinary tract (10 papillomas and 7 carcinomas). Fourteen of these were diagnosed primarily by cytology studies. Most of the patients were completely asymptomatic.

Pulmonary applications

The next largest, non-genital use is the study of specimens from the respiratory tract. Deep cough sputum constitutes the bulk of

these specimens, but bronchial aspirates, washings, and brushings are also frequently submitted. A more sophisticated technique for obtaining specimen material from pulmonary tissue is the percutaneous needle biopsy. This technique is reserved for special cases in which the existence of a lesion and its site are known but a definitive diagnosis has not been made. Pulmonary needle biopsy is done under radiologic control by a well-qualified person, the collected material spread on a slide, immediately fixed, and stained for microscopic examination.

A good candidate for pulmonary cytologic study—beginning with an examination of deep cough sputum—is the middle-aged smoker, man or woman, who complains of chronic cough with blood-tinged sputum. So is the patient whose routine chest x-ray study shows an infiltrate of uncertain cause. If cytology detects malignant cells, it is frequently possible to classify the histologic type of tumor by the cellular morphology. Such identification may be important to the treatment choice.

The practicality of pulmonary cytologic examination as a screening test for the asymptomatic general public is now being investigated. A 5-year project, the National Lung Program, began simultaneously in three medical centers a short time ago with the aim of detecting cancers of the lung while they are still early and curable. The men to be screened in this study are 45 years of age or older and smoke one or more packs of cigarettes a day. They will be examined by special chest x-ray studies yearly; and half of them will receive sputum cytology studies 3 times a year. In a preliminary report of his findings to



Dr. Seybolt is director of the Papanicolaou cytology laboratory and its school of cytotechnology at The New York Hospital-Cornell Medical Center. He is also clinical professor of pathology.

KEFZOL® (cefazolin sodium)

Indications: Kefzol is indicated in the treatment of the following serious infections due to susceptible organisms:

Respiratory tract infections due to *Streptococcus (Diplococcus) pneumoniae*, *Klebsiella* species, *Haemophilus influenzae*, *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant), and group A beta-hemolytic streptococci

Injectable benzathine penicillin is considered to be the drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever.

Kefzol is effective in the eradication of streptococci from the nasopharynx; however, data establishing the efficacy of Kefzol in the subsequent prevention of rheumatic fever are not available at present.

Genitourinary tract infections due to *Escherichia coli*, *Proteus mirabilis*, *Klebsiella* species, and some strains of *Enterobacter* and enterococci

Skin and soft-tissue infections due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci and other strains of streptococci

Bone and joint infections due to *Staph. aureus* septicemia due to *Str. pneumoniae*, *Staph. aureus* (penicillin-sensitive and penicillin-resistant), *Pr. mirabilis*, *Esch. coli*, and *Klebsiella* species

Endocarditis due to *Staph. aureus* (penicillin-sensitive and penicillin-resistant) and group A beta-hemolytic streptococci

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Kefzol.

Contraindication: Kefzol is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE CEFZOLIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SEVERE ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Antibiotics, including Kefzol, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Usage in Infants—Safety for use in premature and infants under one month of age has not been established.

Precautions: If an allergic reaction to Kefzol occurs, the drug should be discontinued and the patient treated with antihistamines, epinephrine or other pressor amines, antihistamines, or corticosteroids.

Prolonged use of Kefzol may result in the overgrowth of nonsusceptible organisms. Careful clinical observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

When Kefzol is administered to patients with low urinary output because of impaired renal function, lower daily dosage is required (see dosage instructions in the package literature).

A false-positive reaction for glucose in the urine may occur with Benedict's or Fehling's solution or with Clinistest® tablets but not with Tes-Tape® (urine sugar analysis paper, Lilly).

Adverse Reactions: The following reactions have been reported: Drug fever, skin rash, vulvar pruritus, eosinophilia, leukopenia, neutropenia, thrombocytopenia, and positive direct and indirect Coombs tests have occurred. Transient rise in SGOT, SGPT, BUN, and alkaline phosphatase levels has been observed without clinical evidence of renal or hepatic impairment. Nausea, anorexia, vomiting, diarrhea, and oral candidiasis (oral thrush) have been reported. Pain at the site of injection after intramuscular administration has occurred, some with induration. Phlebitis at the site of injection has been noted. Other reactions have included genital and anal pruritus, genital moniliasis, and vaginitis.

Administration and Dosage: Kefzol may be administered intramuscularly or intravenously after reconstitution. See the package literature for reconstitution procedures.

See the package literature for dosage recommendations. [022775A]



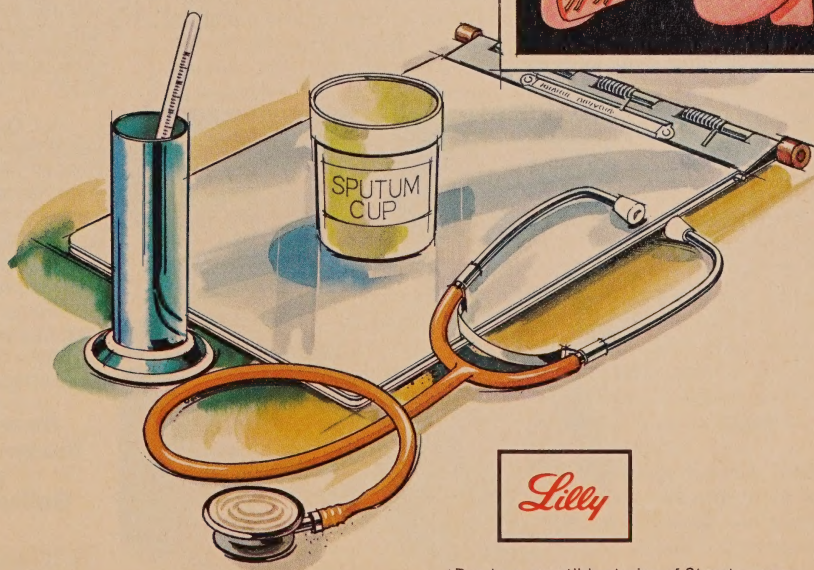
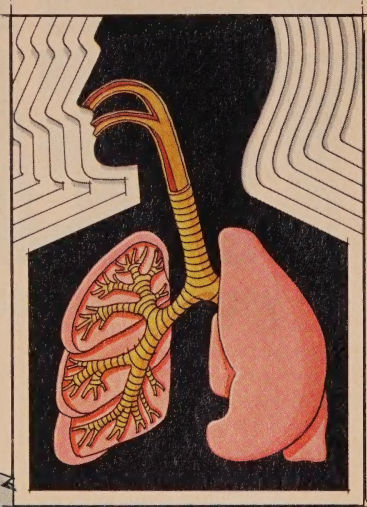
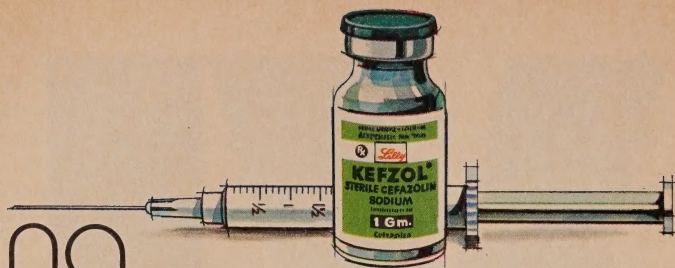
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in treating
acute bacterial
pneumonias*,
the answer
may be

Ampoules, equivalent to 500 mg.
and 1 Gm. of cefazolin

Kefzol[®]
cefazolin sodium



Lilly

*Due to susceptible strains of *Streptococcus* (*Diplococcus*) *pneumoniae*, *Klebsiella* species, *Hemophilus influenzae*, and *Staphylococcus aureus* (penicillin-sensitive and penicillin-resistant).

Please see accompanying page for summary of prescribing information.

V.I.P. THE TREATMENT*

for your menopausal Vasomotor Instability Patients is

BELLERGAL-S™

TABLETS

Each Bellergal-S Tablet contains: phenobarbital, USP central sedative (Warning: May be habit forming), 40.0 mg; Gynergen® (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellafoline® (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.



Long clinical experience has established the effectiveness of Bellergal-S Tablets in menopausal disorders characterized by exaggerated autonomic response—hot flashes, sweats, restlessness and insomnia.

Because Bellergal-S reduces autonomic hyperactivity, a beneficial vaso-stabilizing effect is achieved.

So when estrogen therapy is undesirable... consider Bellergal-S Tablets.

*The Vasomotor Instability Patient treatment—when vasomotor instability is due to exaggerated autonomic response.

BELLERGAL-S™ TABLETS

Composition: Each Bellergal-S Tablet contains: phenobarbital, USP central sedative (Warning: May be habit forming), 40.0 mg; Gynergen (ergotamine tartrate, USP) sympathetic inhibitor, 0.6 mg; Bellatoline (levorotatory alkaloids of belladonna, as malates) parasympathetic inhibitor, 0.2 mg.

Properties and Therapeutics: Based on the concept that functional disorders frequently involve hyperactivity of both the sympathetic and parasympathetic nervous systems, the ingredients in Bellergal are combined to provide a balanced preparation designed to correct imbalance of the autonomic nervous system. The integrated action of Bellergal is effected through the combined administration of ergotamine and the levorotatory alkaloids of belladonna, specific inhibitors of the sympathetic and parasympathetic respectively, reinforced by the synergistic action of phenobarbital in dampening the cortical centers.

Indications: Bellergal is employed in the management of disorders characterized by nervous tension and exaggerated autonomic response:

Menopausal disorders with hot flashes, sweats, restlessness and insomnia.

Cardiovascular disorders with palpitation, tachycardia, chest oppression and vasomotor disturbances.

Gastrointestinal disorders with hypermotility, hypersecretion, "nervous stomach," and alternately diarrhea and constipation.

Genitourinary—uterine cramps, etc.

Premenstrual tension

Interval treatment of recurrent, throbbing headache.

Contraindications: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis, third trimester of pregnancy and glaucoma. Hypersensitivity to any of the components.

Precautions: Even though the ergotamine tartrate content of this product is extremely low and untoward effects have been rare and insignificant, caution should be exercised if large or prolonged dosage is contemplated, and physicians should be alert to possible peripheral vascular complications in patients highly sensitive to ergot. Due to presence of a barbiturate, may be habit forming.

Side Effects: Blurred vision, dry mouth, flushing, drowsiness occur rarely.

Dosage: Bellergal-S Tablets: One in the morning and one in the evening.

How Supplied: Bellergal-S Tablets (compressed, scored tablets of tricolored pattern: dark green, orange and light lemon yellow) in bottles of 100.

Dorsey
LABORATORIES
Division of Sandoz, Inc.
LINCOLN, NEBRASKA 68501

date (after 18 months), one of the investigators in this study has reported twice as many cases of cancer as had been expected. In 6600 men studied, he found 61 cases of suspected or proven pulmonary cancer. *None of the men with positive cytology had any symptoms suggesting cancer.* Undoubtedly, similar programs will eventually be undertaken to determine the efficacy of such testing for neoplasms of other parts of the body in people without symptoms.

Gastrointestinal tract

Cytologic testing can help in the diagnostic investigation of the esophagus, stomach, duodenum (including its related ducts), and the colon. Unfortunately, collecting satisfactory specimens from the gastrointestinal tract is technically more complicated than the collection of many other types of specimens. Collecting such specimens requires intubation, not only for aspiration of the cellular material itself, but also for the necessary preliminary cleansing, and so is not usually readily acceptable to the patient. For this reason alone, gastrointestinal mass screening of symptomless people by this technique is not likely to become very popular. Furthermore, certain procedural details regarding the collection of such specimens are critical for worthwhile results.

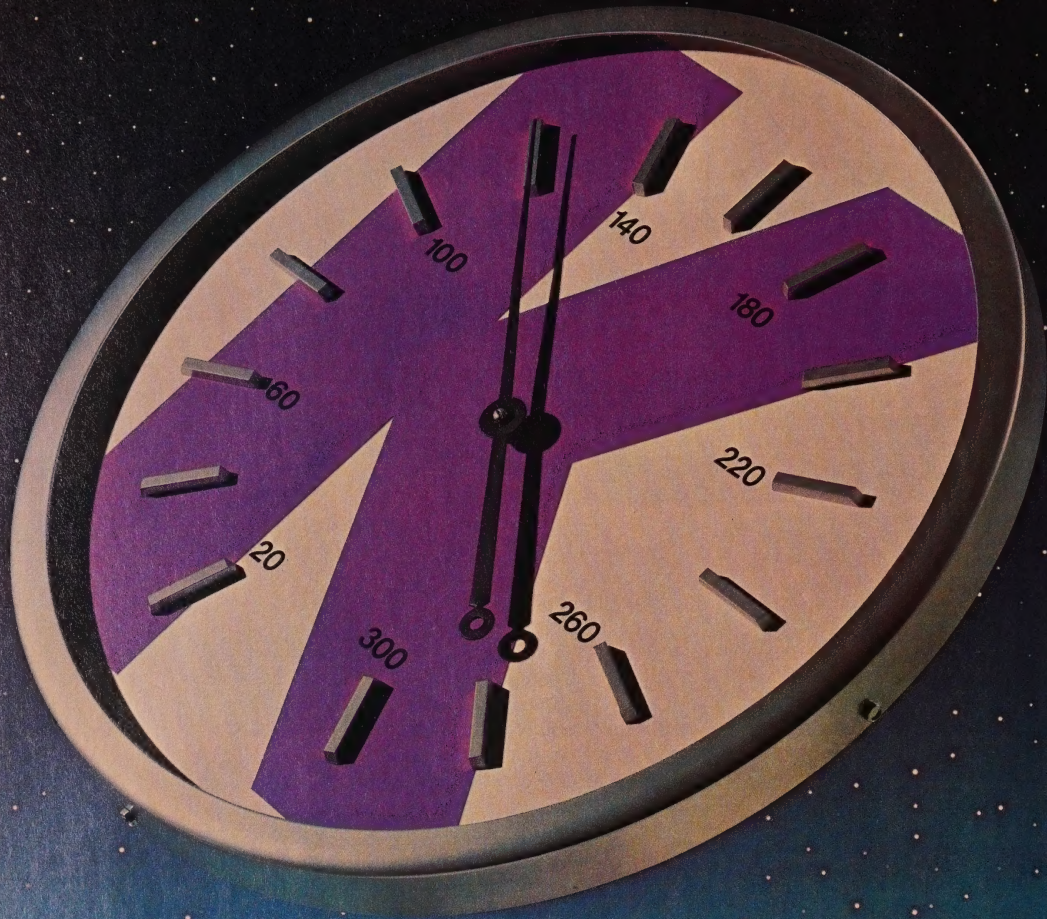
Despite these drawbacks, gastrointestinal cytology has proved to be very useful in many instances. For example, dysphagia is a common indication for an esophageal washing or brushing for the harvesting of cells for cytopathologic study. If tumor cells are found, they can usually be identified as squamous or glandular.

Most medical personnel in-

involved in gastric cytology agree that best results occur when the collection of specimens is assigned to specially designated personnel who become skilled by doing the same procedure over and over—rather than by the busy resident or nurse who might do such a procedure only once in a while. The indications for submitting a gastric specimen to the cytology laboratory are many. One example is an equivocal finding on an upper gastrointestinal series.

Overall, the results with gastric cytology have been roughly comparable to radiologic techniques. As might be expected, cytology has supplied a positive diagnosis in many cases where the x-ray results were negative. One series of patients included 14 cases with proven cancers of the stomach which were detected by cytology but not by x-ray study. You would expect that such cases would naturally be early neoplasms in which treatment would be particularly effective. Actually, of those 14 patients only two were alive at the time of the report (one 2 years and the other 7 years after gastrectomy; the rest presumably died of their cancers). The lesion in both survivors was limited to the epithelium. Why radiology failed to detect cancer in the others was not explained. A fairly recent development in gastric cytology is the use of the fibergastroscope which permits the collection of more selective specimens under direct visualization. Proponents of this technique claim a higher degree of accuracy than is possible by blind aspiration.

Colon specimens also require preliminary cleansing of the area under investigation and meticulous care in the collection and handling of cytologic material



to help reduce blood pressure*
and prevent K^+ loss[†]

consider
ALDACTAZIDE[®]

(spironolactone 25 mg./
hydrochlorothiazide 25 mg.)

- minimizes thiazide-induced potassium loss[†]
- helps avoid costly potassium supplements
- helps improve patient compliance

*In patients with essential hypertension for whom other measures are considered inadequate or inappropriate. Fixed-dose combination drugs are not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management.

†In treating hypertensive patients who have diuretic-induced hypokalemia, when other measures are considered inappropriate.

Before prescribing Aldactazide, please refer to the complete prescribing information, a brief summary of which appears on the next page.

Aldactazide®

(spironolactone 25 mg/
hydrochlorothiazide 25 mg.)

WARNING

Spironolactone, an ingredient of Aldactazide, has been shown to be a tumorigen in chronic toxicity studies in rats (see *Warnings*). Aldactazide should be used only in those conditions described under *Indications*. Unnecessary use of this drug should be avoided.

Fixed-dose combination drugs are not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Indications: Cirrhosis of the liver accompanied by edema and/or ascites; essential hypertension; edema of congestive heart failure and the nephrotic syndrome, when other measures are considered inappropriate.

Contraindications: Anuria, acute renal insufficiency, significant impairment of renal function, hyperkalemia or acute or severe hepatic failure. Allergy to thiazide diuretics or to other sulfonamide-derived drugs.

Warnings: Excessive potassium intake may cause hyperkalemia. Electrolyte imbalances should not be given with Aldactazide. Do not administer concurrently with other potassium-sparing diuretics. Sulfonamide derivatives including thiazides have been reported to exacerbate or activate systemic lupus erythematosus.

Spironolactone has been shown to be a tumorigen in chronic toxicity studies in rats. In one study using 25, 75 and 250 times the usual daily human dose (2 mg./kg.) there was a statistically significant dose-related increase in benign adenomas of the thyroid and testes. In female rats there was a statistically significant increase in malignant mammary tumors at the mid-dose only. In male rats there was a dose-related increase in proliferative changes in the liver. At the highest dosage level (500 mg./kg.) the range of effects included hepatocellular, hyperplastic nodules and hepatocellular carcinoma; the last was not statistically significant.

Precautions: Patients should be carefully evaluated for possible disturbances of fluid and electrolyte balance. Hyperkalemia may occur in patients with impaired renal function or excessive potassium intake and can cause cardiac irregularities which may be fatal. Hyperkalemia may develop as a result of profound diuresis, particularly when Aldactazide is used concomitantly with loop diuretics, glucocorticoids or ACTH. Transient elevation of BUN may occur. Dilutional hyponatremia or rarely low-salt syndrome may develop. Gynecomastia may develop and in rare instances cause breast enlargement may persist.

Thiazides may alter the metabolism of uric acid and carbohydrates with possible hyperuricemia, gout and decreased glucose tolerance. Vascular responsiveness to norepinephrine is reduced. Thiazides may also increase the responsiveness to tubocurarine. Thiazides may decrease serum PBI levels and prolonged therapy may induce hypercalcemia and hypophosphatemia.

Spironolactone may and hydrochlorothiazide does cross the placental barrier. Use in pregnant women requires that the anticipated benefit be weighed against possible hazards to the fetus. Breast feeding should be discontinued when Aldactazide is being used.

Adverse Reactions:

Associated with spironolactone: Gynecomastia is observed not infrequently. Gastrointestinal symptoms include cramping and constipation, drowsiness, lethargy, headache, maculopapular or erythematous cutaneous eruptions, urticaria, mental confusion, drug fever, ataxia, inability to achieve or maintain erection, irregular menses or amenorrhea, postmenopausal bleeding, hirsutism and deepening of the voice. Carcinoma of the breast has been reported but a cause-and-effect relationship has not been established.

Associated with thiazides: Gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, abdominal cramps), purpura, thrombocytopenia, leukopenia, agranulocytosis, dermatologic symptoms (cutaneous eruptions, pruritus, erythema multiforme), paresthesia, acute pancreatitis, jaundice, dizziness, vertigo, headache, xanthopsia, photosensitivity, necrotizing angitis, aplastic anemia, orthostatic hypotension, muscle spasm, weakness and restlessness.

Adverse reactions are usually reversible upon discontinuation of Aldactazide.

Dosage and Administration

Edema in adults: The usual maintenance dose is one tablet four times daily but may range from one to eight tablets daily depending on the response to the initial titration.

Edema in children: The usual daily maintenance dose should be that which provides 0.75 to 1.5 mg. of spironolactone per pound of body weight (1.65 to 3.3 mg./kg.).

Essential hypertension: Usually two to four tablets daily depending on results of the titration of the individual ingredients.

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Medical Communications Department

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for a satisfactory examination. Several techniques have been described for collecting and preparing a colon specimen. An interesting method was reported by Katz who uses saline lavage with simultaneous suction. His results were excellent for patients whose lesions were within range of the sigmoidoscope. In patients with sigmoid lesions beyond 25 cm, the results were predictably less impressive, but they still certainly justify the continued use of colon cytology studies.

Exudates and fluid

Strictly speaking, examining the cellular content of exudates (chiefly pleural, peritoneal, and pericardial fluids) and of cerebrospinal fluid does not qualify as a "Pap test" since each such examination was common practice long before Papanicolaou devised the Pap test. However, the laboratory techniques, and certainly the staining, were somewhat different. In the case of cerebrospinal fluid, the examinations used to be concerned mainly with inflammatory rather than malignant cells. In the study of exudates, the paraffin cell block was the usual technique. It is probably fair to say that the evaluation of these sections stressed their architectural arrangement (much as with a tissue section) rather than their nuclear and cytoplasmic characteristics. Papanicolaou pointed out that such cellular characteristics could often be diagnostic even when based on relatively few cells. The detection of malignant cells in exudates obviously plays no role in early diagnosis, but it can help determine the underlying cause of ascites, pleural effusion, and other conditions, and so may well dictate the type of therapy. Again, cytology can

help evaluate the response to treatment.

Neurologic cytology has become part of the routine in many laboratories where a search for cancerous cells is the primary function. Specimens of cerebrospinal fluid may be collected by lumbar puncture, ventricular tap, or aspiration with a device such as an Ommaya reservoir. We prefer to use the cytocentrifuge in the preparation of specimens. The cytopathologist can detect primary as well as metastatic tumors of the central nervous system, provided the neoplasm in the brain or cord is located in a site that permits the sloughing of some of its cells into the fluid. Such cytology studies may solve the diagnostic problem of differentiating a cerebrovascular accident and a tumor.

Neurologic cytology studies can also help evaluate the results of treatment. Acute lymphocytic leukemia is a good case in point. To quote the Hajdus¹: "One of the best examples of the usefulness of cytologic examination is in the diagnosis of leukemic involvement of the central nervous system." ... "Since it is possible today to control the diseases, and since patients with acute leukemia can be kept alive for long periods with adequate therapy, it is essential that the course of the disease and its therapy be monitored by cytologic examination at regular intervals."

Miscellaneous specimens

Cytology studies can also be adapted to various other body fluids. Nipple secretion, cyst aspirations, surgical wound secretions, joint and even ocular fluids are some of the miscellaneous specimens submitted for cytologic examination, not nec-

¹ Hajdus SI, Hajdus E: *Cytopathology of Sarcomas*. Philadelphia, WB Saunders, 1976.

essarily for detecting malignant cells alone, but also for whatever other information can be obtained from their cellular content.

Non-malignant cytology

Many non-malignant conditions produce recognizable cellular changes. One such change is inflammation caused by various agents such as viruses, including cytomegalic inclusion disease and genital herpes which can cause reliably characteristic cellular changes. Fungal forms are also frequently identified. Often they are merely contaminants, but some may, indeed, be pathogenic, and reporting their presence can lead to correct therapy. One example is *Cryptococcus neoformans* in cerebrospinal fluid. Rheumatoid arthritis sometimes produces a "unique inflammatory picture" in pleural fluids which can be recognized during a routine cytologic examination of the effusion. Also, from time to time, cytopathologists are called upon to express an opinion concerning an individual's genetic sex based on the percentage of Barr bodies in the cells of a buccal scraping.

How accurate?

The accuracy of exfoliative cytology in diagnosing malignant neoplasms is difficult to evaluate because of the numerous variables. For instance, published reports from different laboratories are difficult to compare because of differences in methods of analysis and variations in the techniques of collecting and processing specimens. The accuracy is also related to the kind of specimen under consideration. Whereas the cytologic studies of specimens from the uterine cervix are highly reliable, studies of specimens from the renal paren-

chyma and prostate are much less so. And, of course, the cytopathologist's own experience with a particular kind of specimen also affects accuracy statistics.

Remember that a negative cytologic report does not by any means assure that the patient is free of cancer. *All it tells is that no malignant cells were seen or recognized in that particular specimen.* As in any laboratory test, false-positive reports do occur, and even experts have been fooled from time to time. Sometimes such misleading reports can be accounted for by pathologic but non-malignant conditions, or by drugs and other types of therapy that can produce confusing cellular changes. Hence, when submitting a specimen, be sure to supply the laboratory with pertinent information concerning the patient's medical history. Be sure to include any factors that might be responsible for morphologic changes in the cellular content of the specimen. Without such information, the cytopathologist "has one hand tied behind his back."

Clearly, we are not yet fully using the potential cytology offers since we are still using its extragenital applications chiefly for working up symptomatic patients in whom tumors may have already outgrown the eradicable stage. Yet, to offer mass cytologic screening to apparently well individuals would tax the present laboratory facilities far beyond their capacity. A promising field is that of automation in cytologic interpretation by various electronic techniques. Should this become a practical reality, it will hasten the day when all men, women, and children will benefit fully from Papanicolaou's legacy.

Macrodantin® (nitrofurantoin macrocrystals)

Capsules 25 mg 50 mg 100 mg

INDICATIONS: Indicated for the treatment of pyelonephritis, pyelitis, and cystitis due to susceptible *E. coli*, enterococci, *S. aureus* (it is not indicated for the treatment of associated renal cortical or perinephric abscesses) and certain strains of *Klebsiella-Aerobacter*, *Proteus* and *Pseudomonas*.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function; infants under one month; pregnant patients at term; known hypersensitivity.

WARNINGS: May cause hemolytic anemia of the primaquine sensitivity type, apparently linked to a glucose-6-phosphate dehydrogenase deficiency. (Such patients should be closely observed while receiving nitrofurantoin.) Discontinue the drug at any sign of hemolysis. Hemolysis ceases on withdrawal. Superinfections (limited to the genitourinary tract) may occur, most commonly due to *Pseudomonas*. Safety not established during pregnancy and lactation; should not be used in women of childbearing potential unless the expected benefits outweigh the possible hazards.

PRECAUTIONS: Peripheral neuropathy may occur. A fatality has been reported. Predisposing conditions such as renal impairment, anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.

ADVERSE REACTIONS: Gastrointestinal Reactions— Anorexia, nausea, emesis are the most frequent reactions; less frequently, abdominal pain and diarrhea; rarely, hepatitis. This dose-related toxicity reaction can be minimized by reduction of dosage, especially in the female patient.

Hypersensitivity Reactions— Pulmonary sensitivity reactions, which can be acute, subacute, or chronic. Acute reaction is commonly manifested by fever, chills, cough, chest pain, dyspnea, pulmonary infiltration with consolidation or pleural effusion on X-ray, and eosinophilia. The acute reactions usually occur within the first week of treatment and resolve with cessation of the drug therapy. Subacute or chronic pulmonary reaction is associated with prolonged therapy. Insidious onset of malaise, dyspnea on exertion, cough, altered pulmonary function, and roentgenographic and histologic findings of diffuse interstitial pneumonitis or fibrosis or both are common manifestations. Impaired pulmonary function may result even after cessation of the drug therapy.

Dermatologic Reactions— Maculopapular, erythematous, or eczematous eruption, pruritus, urticaria, and angioedema.

Other Sensitivity Reactions— Anaphylaxis, asthmatic attack in patients with history of asthma, cholestatic jaundice, drug fever, and arthralgia.

Hematologic Reactions— Hemolytic anemia, granulocytopenia, leukopenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.

Neurological Reactions— Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness.

Miscellaneous Reactions— Transient alopecia.

SUPPLIED: Macrocrystalline (nitrofurantoin macrocrystals) is available in opaque, yellow capsules of 100 mg (coded "Eaton 009") and in opaque, yellow and white capsules of 50 mg (coded "Eaton 008") in bottles of 30, 100, 500, and 1,000 capsules; and in opaque, white capsules of 25 mg (coded "Eaton 007") in bottles of 100 capsules. Macrocrystalline Capsules, 50 mg and 100 mg, are also available in hospital unit-dose packages, strip-packaged in boxes of 100.



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Recurrent UTI* in the Sexually Active Female

Special Problems of Management



A. General measures

- Showering rather than tub-bathing
- Showering before intercourse
- Voiding after intercourse

B. Antimicrobial therapy

■ Overt episodes of urinary tract infection* should be treated with a standard course of Macrochantin® therapy, until there is evidence of bacteriologic cure.

However, for the women who have recurrent UTI associated with sexual intercourse, *long-term suppressive therapy* is recommended, including...

■ **Nightly antibacterial therapy:** An oral dose at bedtime for several months or longer (one 50 mg or one 100 mg Macrochantin® capsule) for the patient who has a continuing "chronic" cystitis. The rationale for the bedtime dose is that during this period the bladder remains unemptied for the longest interval.



Capsules
25 mg 50 mg 100 mg

Macrochantin® (nitrofurantoin macrocrystals)

**Consistent potency against the
most prevalent uropathogens**

*Macrochantin® is effective in cystitis, pyelitis and pyelonephritis due to susceptible organisms. See brief summary on facing page.

How to correct childhood hypertension

Bonita Falkner, M.D.

More and more we are realizing that hypertension—with its potential for vascular and target organ damage—is not uncommon in children. Since this is so, it becomes more important than ever to check blood pressure in children and to identify and follow children with a potential risk for development of hypertension.

Taking a child's pressure

A child's blood pressure can generally be determined by standard sphygmomanometry. Blood pressure cuffs are available in infant and child sizes. For extremely obese adolescents, extra large leg cuffs are available.

The child should be relaxed and calm, sitting or supine during the procedure. Very young children may prefer sitting on the parent's lap. Reassure the child that he will feel no discomfort.

The width of the cuff should cover about two thirds of the upper arm, measured from shoulder to elbow. The inflatable part of the cuff should cover at least one half of the arm circumference.

Once you determine the pressure, the next question is whether that pressure is normal for that particular child. A pressure of 135/80 mm Hg may be normal for a well-developed adolescent boy, but it is not normal for an 18-month-old child. A rule of thumb to follow is that any child under 8 years old should have a diastolic pressure of less than 80 mm Hg; and under 4 years old, a diastolic pressure of less than 70 mm Hg.

Secondary hypertension

Seek out the underlying cause for significant hypertension in any child showing it. Essential hypertension is less commonly manifested in childhood. However, children with other disorders (including certain congenital anomalies, malignancies, and endocrine disorders) show hypertension as a response to the primary disease state. These patients are at risk not only from the sustained hypertension but also from the primary disease itself (as, for example, from Wilms' tumor or hyperthyroidism).

To ease the task in tracking down the pathology involved, consider the causes of child-

NOW FROM 

For the treatment of depression

PAMELOR[®]

(nortriptyline HCl) NF
25mg. Capsules



Provides 2 important benefits for both patients and clinicians.

- PAMELOR[®] begins to improve sleep patterns within a week.
- PAMELOR[®] allows patients to remain calm yet alert.

For Brief Summary please see following page.

NOW FROM  **SANDOZ**

PAMELOR®

(nortriptyline HCl) NF
25 mg. Capsules

The antidepressant with 2 important clinical benefits

PAMELOR® begins to improve sleep patterns within a week

● PAMELOR® helps relieve the sleep problems that accompany depression: difficulty in falling asleep, restless sleep, and early-morning awakening. An improved pattern of sleep begins to appear in some patients within the first week of therapy.

● Overall improvement is often observed by the end of the second week. Maximum improvement with Pamelor®, as with other antidepressants, may require a longer period of therapy, particularly in severe depressive illnesses.

Indications: For relief of depressive symptoms. Endogenous depressions are more likely to be alleviated than others.

Contraindications: Hypersensitivity. Should not be given concomitantly with MAO inhibitors or within 2 weeks of the use of this drug since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations. Cross-sensitivity with other dibenzazepines is a possibility. Contraindicated during acute recovery period after myocardial infarction.

Warnings: Use with caution in patients with cardiovascular disease because of tendency to produce sinus tachycardia and prolong conduction time. Myocardial infarction, arrhythmia, and strokes have occurred. May block antihypertensive action of guanethidine and similar agents. Because of anticholinergic activity, use cautiously in patients with glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely because the drug is known to lower the convulsive threshold. Great care is required for hyperthyroid patients and those taking thyroid medication because of possible development of cardiac arrhythmia. Caution patients about possibility of impaired mental and/or physical ability to operate a motor vehicle or dangerous machinery. Response to alcoholic beverages may be exaggerated and may lead to suicidal attempts. Safe use during pregnancy, lactation, and women of childbearing potential has not been established and the drug should not be given unless clinical situation warrants potential risk. Not recommended for use in children.

Precautions: Psychotic symptoms may be exacerbated in schizophrenic patients. Increased anxiety and agitation may occur in overactive or agitated patients. Manic-depressive patients may experience shift to manic phase. Hostility may be aroused. Concomitant administration of reserpine may produce a "stimulating" effect. Watch for possible epileptiform seizures during treatment. Use cautiously with anticholinergic or sympathomimetic drugs. Concurrent electroconvulsive ther-

apy may increase hazards associated with nortriptyline HCl. When possible, discontinue drug several days prior to surgery. Potentially suicidal patients require supervision and protective measures during therapy. Prescriptions should be limited to the least possible quantity. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: Note: The pharmacologic similarities among the tricyclic antidepressant drugs require that each of the following reactions be considered when nortriptyline is administered. **Cardiovascular:** Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation, insomnia, panic, nightmares; hypomania; exacerbation of psychosis.

Neurologic: Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; finitius.

Anticholinergic: Dry mouth and rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract.

Allergic: Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs.

Hematologic: Bone-marrow depression, including agranulocytosis; eosinophilia; purpura; thrombocytopenia.

Gastrointestinal: Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue.

Endocrine: Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels.

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● PAMELOR® also has a mild calming action to help relieve the anxiety and tension that are often symptoms of depression. Because PAMELOR® rarely causes excessive drowsiness, patients are more alert and better able to function. Nevertheless, they should be cautioned about driving or operating machinery.

Other: Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia.

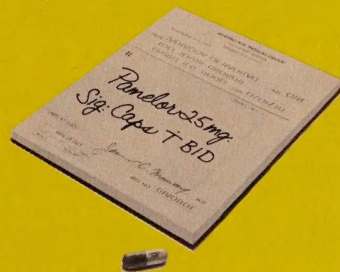
Withdrawal Symptoms: Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Dosage and Administration: *Usual adult dose*—25 mg. three or four times daily; dosage should begin at a low level and increase as required. *Elderly and Adolescent:* 30 to 50 mg. per day, in divided doses. Doses above 100 mg. per day and use in children are not recommended. If a patient develops minor side effects, the dosage should be reduced. The drug should be discontinued promptly if adverse effects of a serious nature or allergic manifestations occur.

How Supplied: Capsules 10 mg. and 25 mg.; solution 10 mg./5 cc.

For more detailed information see full prescribing information. SDZ-79

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hood hypertension in terms of frequency of occurrences and system involvement. Then divide the causes into those which can be corrected and those which cannot.

Some acute childhood illnesses also produce hypertension, and the elevated pressure disappears upon resolution of the acute illness.

About half the hypertension in children is caused by underlying kidney or urinary tract disorders. These disorders include unilateral renal lesions, such as unilateral hydronephrosis and unilateral hypoplastic kidney, or congenital obstructions, embryologic abnormalities, and unilateral pyelonephritis. After the underlying anomaly has been corrected, chances for curing the hypertension are good. Wilms' tumor, other renal tumors, and renal trauma are also associated with hypertension. All are potentially correctable.

Cardiovascular lesions associated with childhood hypertension are patent ductus arteriosus and coarctation of the thoracic aorta. Coarctation

may also occur in the abdominal aorta. Renal vascular anomalies may also be seen and may be associated with other disorders such as neurofibromatosis.

Endocrine disorders are less commonly a cause of hypertension. However, Cushing's disease, hyperthyroidism, primary aldosteronism, and adrenogenital syndrome in childhood all may manifest hypertension. This also holds true for neuroblastoma and pheochromocytoma, malignancies of childhood. Pheochromocytoma is very rare. However, when present, it manifests itself in preadolescents, with sustained rather than episodic hypertension.

Miscellaneous causes of correctable hypertension include exogenous administration of glucocorticoids. Excessive licorice ingestion is also a possible cause of hypertension. Here, the culprit is glycyrrhetic acid, which is biochemically similar to desoxycorticosterone. In excess, this acid induces a clinical syndrome similar to hyperaldosteronism. American manufacturers of licorice have artificially flavored their product, thus protecting the most avid licorice consumer.

Uncorrectable hypertension

Uncorrectable or chronic causes of hypertension include chronic bilateral renal disorders, such as bilateral chronic glomerulonephritis, bilateral chronic pyelonephritis, and polycystic kidney disease. Collagen vascular diseases with renal involvement are also included. Uncorrectable vascular lesions are quite rare. They include bilateral renal artery abnormalities, which are technically impossible to correct surgically,

and hypoplasia of the aorta. Essential hypertension is also included as a miscellaneous cause of chronic hypertension. It is fairly uncommon in early childhood, but it is one of the more common causes in adolescence. Other potential, but fairly uncommon causes, are post-irradiation parenchymal damage, lead nephropathy, and porphyria.

Acute hypertension

Various disease states occur in which the onset of the hypertension is sudden and persists until resolution of the primary disease. These include renal disorders, such as acute glomerulonephritis and hemolytic-uremic syndrome. Children undergoing genitourinary tract surgery tend also to develop transient postoperative hypertension.

Acute disease processes of the central nervous system which result in increased intracranial pressure (such as meningitis or space-occupying lesions) may result in acute hypertension. Burns may also be associated with an acute elevation of blood pressure. In all these disorders, the hypertension should be controlled medically until the underlying disease contributing to the hypertension has been resolved.

Essential hypertension

Heredity is generally thought to be a major determinant in the development of essential hypertension in adults, which is more common among blacks than among whites in this country. In addition to a strong family history of hypertension, other factors are closely associated with adult hypertension, including obesity, a high intake of salt, stress, and environmental



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MEDICAL DIRECTOR'S PAGE

Bruce H. Medd, M.D., Director, Professional Services

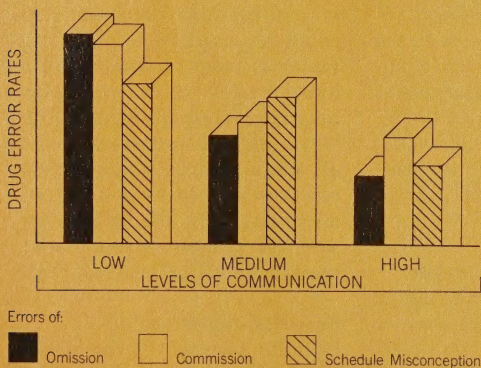


Although prior discussions of timely issues on this page have centered on psychoactive drugs, we would now like to address a problem of major importance that pervades all areas of medicine...

Noncompliance

Estimates of the rate of patient noncompliance range from 30 to 50%.^{1,2} As you well know, non-compliance with prescription medication can take various forms—premature discontinuance, errors of omission and commission, erratic dosing, mistakes in timing or sequence, and misuse of medications. Causative factors include lack of knowledge or understanding, patient personality, erroneous information derived from nonmedical sources and poor health attitudes and beliefs.

One group of researchers at the University of North Carolina took a closer look at noncompliance errors in 357 patients with diabetes mellitus or congestive heart failure and clearly linked level of physician-to-patient communication with drug error rate.^{3,4} Conversely, this same study also found that adequate knowledge of a drug's function was associated with a decrease in errors of commission and misconception of dosage schedules.



Errors of:

■ Omission □ Commission ▨ Schedule ▩ Misconception

Opportunities to enhance patient knowledge and understanding can begin with the physician at the time of initial prescribing, be reinforced by the pharmacist at the time the prescription is filled and continued by the physician or his assistant at the follow-up visits. The following are some suggestions for promoting compliance in those patients that you feel may have a problem complying:*

- if feasible, discuss clearly with the patient what is wrong with him, what the treatment regimen is, what he can expect from it and the possible problems or pitfalls
- encourage patient questions regarding therapy
- consider patient attitudes and beliefs which might affect compliance
- confirm that the patient understands what is expected of him and emphasize the importance of compliance
- reinforce important instructions in writing if possible
- enlist family support where available
- set definite appointment dates for follow-up visits
- ascertain patient compliance status at each visit and identify reason for noncompliance if this is noted
- formulate a plan, with patient's cooperation, for correcting noncompliance

One leading authority in the field of patient compliance feels that "...the importance of open communication between patient and physician cannot be overemphasized." And we heartily agree with his conclusion that: "...perhaps the most important aspect of patient compliance—[is] what patient and physician can learn from each other for the better management of the disease."⁵

*If you would like a brochure containing a series of articles on the nature, incidence and causes of noncompliance by a leading specialist in this area, as well as appropriate techniques for correcting or preventing it, just ask your Roche representative or write to me: Bruce H. Medd, M.D., Director of Professional Services, Roche Laboratories, Division of Hoffmann-La Roche Inc., Nutley, N.J. 07110

1. Davis MS: *Am J Public Health* 58: 274-288, 1968 2. Davis MS: *J Med Educ* 41: 1037-1048, 1966 3. Hulka BS et al: *J Chronic Dis* 28: 7-21, 1975 4. Hulka BS et al: *Am J Public Health* 66: 847-853, 1976 5. Weintraub M: *Med Challenge* 9: 61-71, 1977

Roche Laboratories
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Nutley, New Jersey 07110

Antihypertensive therapy for children

Drug	Route	Onset of effects	Dosage
Reserpine	I.M.	2 hours	0.2 mg test, then 0.02 mg/kg every 4 to 6 hours (max. 0.5 mg/day)
	Oral	3 to 7 days	0.005 to 0.015 mg/kg/day (0.25 to 0.5 mg max./day)
Methyldopa	I.V.	2 to 6 hours	60 to 1000 mg
	Oral	4 to 6 hours	10 to 60 mg/kg/day
Hydralazine	I.V.	Immediate	0.15 mg/kg every 4 to 6 hours
	I.M.	15 to 20 minutes	0.25 mg/kg every 4 to 6 hours
	Oral	2 to 4 hours	0.2 to 0.6 mg/kg every 4 to 6 hours
Guanethidine	Oral	36 to 48 hours	0.2 to 2.5 mg/kg/day
Propranolol	Oral	24 to 36 hours	0.2 to 2 mg/kg/day
Diazoxide	I.V.	5 to 15 minutes	5 mg/kg
Chlorothiazide	Oral	7 days	10 to 20 mg/kg/day
Spironolactone	Oral	7 days	1 to 10 mg/kg/day
Furosemide	Oral	1 hour	2 to 8 mg/kg/day

factors. Precisely how these external factors generate essential hypertension remains unclear at this time.

The hypothesis that the course of essential hypertension evolves through an early phase of labile hypertension marked by a hyperkinetic cardiovascular state is being increasingly accepted. Recently, essential hypertension has been found in significant numbers of obese black adolescents suggesting that multiple risk factors actually induce an earlier onset of the disease.

Labile hypertension

Labile hypertension is characterized by episodes of blood pressure elevation followed by normal pressures and later elevations. This finding, along with a family history of hypertension, identifies a child who may be at risk for later essential hypertension. Potential risk factors in children for develop-

ment of hypertension include a family history of the disease, labile blood pressure, obesity, and a high intake of dietary salt. Thus, a child with a strong family history of hypertension and one or more additional risk factors should be observed closely. Early detection and treatment of sustained hypertension may result in a more easily manageable form of the disease.

Evaluation

When evaluating a child with elevated pressure, try to determine the underlying cause. Unless the hypertension is secondary to some correctable underlying cause, the child has a chronic disease that must be managed indefinitely with medical therapy.

The extent to which you subject a child to an extensive investigation should depend on the severity of the hypertension, the age of the child, and

any associated disease state. For example, a young child with a blood pressure of 150/100 mm Hg should be studied exhaustively for a cause, while an obese 14-year-old with blood pressure readings of 140/90 and a parent with hypertension may be evaluated more briefly. Similarly, a child with sudden elevation of blood pressure associated with confirmed post-streptococcal acute glomerulonephritis may not need to undergo further study unless the blood pressure remains high after the acute process.

A careful medical history, including family history, and a physical examination are the first steps. Any acute process associated with hypertension can frequently be determined on this basis alone. Also, other signs, such as a cardiac murmur or abdominal mass, may be found, giving the direction for further evaluation.

If no clues appear in the

history or physical examination to suggest any system involvement to account for the blood pressure elevation, you must rely on further laboratory investigation. The extent to which laboratory and other special studies should be pursued depends on the age and severity of hypertension. Children with blood pressures beyond the 95th percentile for age and adolescents with blood pressures greater than 140/100 mm Hg should be investigated thoroughly. Studies should include:

- Blood count
- Urinalysis and culture, and urine electrolytes
- Serum electrolytes, creatinine, and plasma cortisol
- Intravenous pyelogram, chest x-ray studies, and electrocardiogram
- 24-hour urine protein excretion and creatinine clearance
- 24-hour urine 17-ketosteroids and 17-hydroxycorticosteroids
- 24-hour urine vanillylmandelic acid
- Arteriography.

If a child has a blood pressure between the 90th and 95th percentiles, or if an adolescent has diastolic pressure between 90 and 100 mm Hg, it may not be necessary to evaluate him so extensively, particularly with a family history of hypertension. A basic evaluation consists of:

- Blood count
- Urinalysis and urine culture
- Serum creatinine
- Intravenous pyelogram
- Electrocardiogram.

Children with labile hypertension or any of the associated risk factors should be observed with periodic pressure determinations and health examinations. If the pressure rises progressively and becomes fixed in a hypertensive range,

they should be further evaluated before medical treatment.

Treatment

The selection of drugs and route of administration in antihypertensive therapy for children are determined by the severity of the condition. A hypertensive crisis with a diastolic blood pressure greater than 110 mm Hg usually requires vigorous therapy with parenteral antihypertensive medication. But a mild-to-moderate hypertension can generally be effectively managed in an outpatient setting with oral medication. The Table lists the various antihypertensive and diuretic medications, with pediatric dosages.

Sudden onset

The child who has a sudden onset of hypertension (with diastolic blood pressures at or beyond 110 mm Hg) is usually symptomatic. The blood pressure should be lowered rapidly. An effective and commonly used drug is intramuscular reserpine. If the response is not sufficient with 2 hours, hydralazine intramuscularly or by intravenous titration may be added, with the two drugs given concurrently thereafter. This combination has been used effectively in children with acute glomerulonephritis or acute renal failure. Occasionally, it is necessary to decrease the blood pressure more rapidly—for example, if a child has seizures from hypertensive encephalopathy. Here, diazoxide provides the most rapid onset of action. A dose of 5 mg/kg is administered over 5 to 15 minutes. Monitor the pressure continuously during administration, until it stabilizes at a lower range. Repeat

the same dose when the pressure rises again, and as often as necessary to maintain pressure at a safe level. In an emergency, methyldopa may also be administered parenterally. However, its action is slower in onset and somewhat less predictable in children.

Moderate hypertension

Children with moderate hypertension (with diastolic blood pressures above 95 mm Hg or beyond the 95th percentile), generally require antihypertensive medication. Unless they are significantly symptomatic they can generally receive oral medication with the dosages adjusted in the office. Methyldopa is somewhat preferable to reserpine for this use, because methyldopa does not have the bothersome side effects of reserpine. Hydralazine may be used as a single agent or in combination with another antihypertensive. For children with a marked tachycardia with their blood pressure elevation, the combination of hydralazine and propranolol is particularly effective. When propranolol is added, the pulse should be checked each week for a few weeks. Diuretics may be added to augment the effects of the blood pressure lowering drugs. In very mild cases, a diuretic such as chlorothiazide may be all that is needed to maintain the blood pressure in a satisfactory range. Along with prescribing drugs, encourage dietary salt restriction—except, of course, for children with both salt-losing nephropathy and hypertension.

Children with labile pressures should be followed so that therapy can be instituted if their pressures reach levels that warrant treatment.

Radiation therapy for plantar warts

Two Maryland radiologists have shown that radiation therapy can provide a safe and effective treatment for plantar warts.

Dr. Stanley Macht and Dr. Jose M. Cordero, Washington County Hospital, Hagerstown, Maryland, have reported an exceptionally high cure rate (Tables 1 and 2) in 360 patients with 531 plantar warts treated with low-voltage radiation. Throughout this 24-year study, not a single complication or adverse effect was observed. They noted that younger patients (under 25 years of age) who received radiation therapy have a much higher chance for complete cure than older patients.

Procedures

After paring the warts, shielding the surrounding area with lead, and carefully draping the patients with lead aprons, Drs. Macht and Cordero radiated 436 lesions with a 250-kilovolt constant potential orthovoltage therapy unit, calibrated at 100 kv with no filter.

In another procedure 95 warts were radiated with a 100-kv superficial therapy unit with no filter. This second procedure

provided superficial radiation that affected the wart but allowed little radiation to penetrate deeper into underlying tissues. It was found, however, to be much less effective in producing total cures.

The course of treatment consisted of a single radiation dose of 1,000 rads in air. Sixty warts that proved resistant to this initial radiation dose were given a course of three additional treatments, totaling 2,000 rads. According to the radiologists' re-

port, follow-up in all cases showed no complications or adverse effects of therapy.

Despite fears among some members of the medical community of overexposure to radiation, and despite occasional reports of radiation ulcers, Drs. Macht and Cordero maintain that "... x-ray therapy as administered under the above described parameters is still one of the most efficient, safe, and easily administered modes of therapy for warts." 

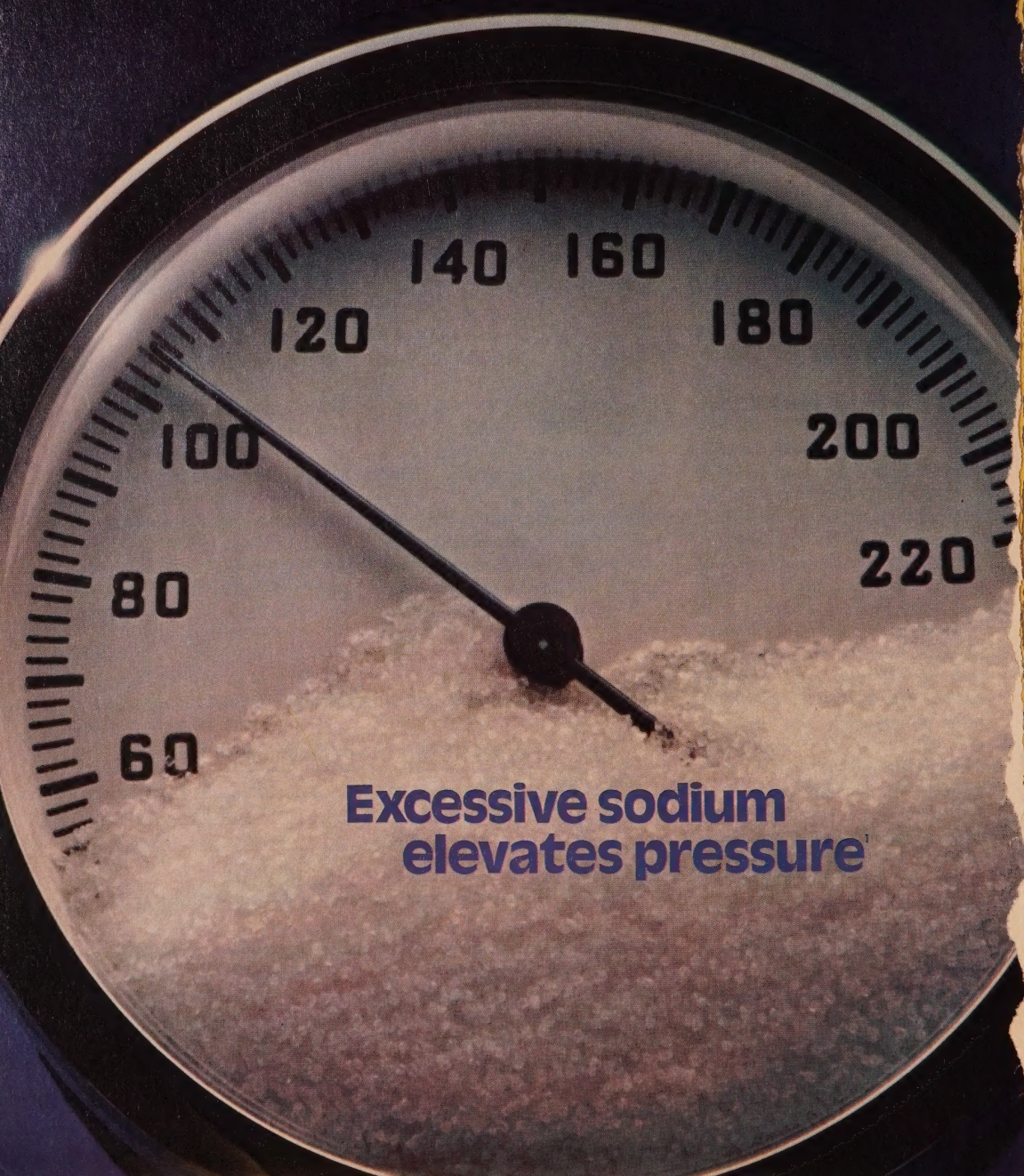
Table 1 — Plantar warts treated with orthovoltage unit

Age	No. treated	% Cured	% Improved	No effect
Under 12	140	97.1	1.5	1.4
13-24	164	90.9	6.1	3.0
Over 25	132	79.2	12.5	8.3

Table 2 — Plantar warts treated with superficial unit

Age	No. treated	% Cured	% Improved	No effect
Under 12	27	84.4	15.6	0
13-24	32	88.2	0	11.8
Over 25	36	41.2	47.1	11.7

In hypertension...



**Excessive sodium
elevates pressure**

Relieving chronic pain without strong analgesics

Part 2—Corticosteroids, psychotropics, anticonvulsants, and placebos

Mary E. Moore, M.D., Ph.D.

In part 1, I talked about non-steroidal anti-inflammatory agents for pain relief. Now I'd like to talk about some other agents for pain relief.

Corticosteroids

Though you should not use corticosteroids systemically on a daily basis, you can use them to good advantage locally, at intervals, for the treatment of painful musculoskeletal complaints. For example, injection of joints, bursae, tendon sheaths, and tender trigger points is very effective. All the glucocorticoid preparations designed for intra-articular use are effective. Some of the most commonly used are triamcinolone acetonide, prednisolone butylacetate, methylprednisolone acetate, and triamcinolone hexacetonide. The usual dose is 0.25 to 1 ml.

Complications of local use include small areas of subcutaneous and cutaneous atrophy and hypo- and hyperpigmentation. If you warn the patient about these ahead of time they are generally of little consequence.

A more troublesome problem is post-injection flare, an exacerbation of pain in the injection area. Fortunately, this is rare and lasts only a few hours.

The more serious problem of primary concern when intra-articular injections are involved is destruction of cartilage or other supportive tissue. To avoid such destruction, do not inject the same area more than once every 2 or 3 months, and continue such therapy for long periods only in exceptional circumstances.

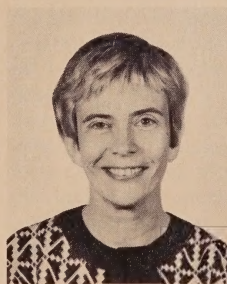
Psychotropic drugs

Since sleeplessness, tension, and depression often accompany and may aggravate pain, you may find that hypnotics, tranquilizers, and antidepressants are useful in the treatment of chronic pain. In addition, drugs originally designed as anticonvulsants have proved useful in pain therapy.

The combination of an antidepressant (amitriptyline) and a tranquilizer (fluphenazine) has brought considerable pain relief to patients with postherpetic neuralgia, peripheral neurop-

athy, pain secondary to demyelinating disease, and pain following cerebral infarction. Also we have found this combination useful for pain secondary to shoulder-hand syndrome, severe osteoarthritis, and low back syndrome. We have even used it with great success to supplement conventional therapy in rheumatoid arthritis.

The therapeutic regimen combines 75 mg of amitriptyline at



Dr. Moore is associate professor of medicine in the section of rheumatology at Temple University Hospital, Philadelphia, and is a member of the Temple University Pain Control Center. She is certified by the American Board of Internal Medicine in internal medicine and rheumatology. In addition to her medical degree, Dr. Moore has a Ph.D. in psychology.



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cephalexin 250-mg. Pulvules[®]
in acute bacterial bronchitis
due to susceptible strains of Streptococcus (Diplococcus) pneumoniae

See adjoining column for summary of prescribing information.

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cephalexin

Indications: Keflex is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *Streptococcus (Diplococcus) pneumoniae* and group A beta-hemolytic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflex is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keflex in the subsequent prevention of rheumatic fever are not available at present.)

Otitis media due to *Str. pneumoniae*, *Hemophilus influenzae*, staphylococci, streptococci, and *Neisseria catarrhalis*

Skin and soft-tissue infections caused by staphylococci and/or streptococci

Bone infections caused by staphylococci and/or *Proteus mirabilis*

Genitourinary tract infections, including acute prostatitis, caused by *Escherichia coli*, *Pr. mirabilis*, and *Klebsiella* sp.

Note: Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Contraindication: Keflex is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to Keflex.

Usage in Pregnancy:—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side-effects or unusual manifestations of drug idiosyncrasy may be detected. If an allergic reaction to Keflex occurs, the drug should be discontinued and the patient treated with the usual agents (e.g., epinephrine or other pressor amines, antihistamines, or corticosteroids).

Prolonged use of Keflex may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs test may be due to the drug.

Keflex should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

Indicated surgical procedures should be performed in conjunction with antibiotic therapy.

As a result of administration of Keflex, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinistest[®] tablets but not with Tes-Tape[®] (Glucose Enzymatic Test Strip, USP, Lilly).

Adverse Reactions: Gastrointestinal—The most frequent side-effect has been diarrhea. It was very rarely severe enough to warrant cessation of therapy. Nausea, vomiting, dyspepsia, and abdominal pain have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema) have been observed. These reactions usually subsided upon discontinuation of the drug. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasis, vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia, neutrophilia, and slight elevations in SGOT and SGPT have been reported.

[032477]

bedtime with 1 mg of fluphenazine 3 times daily. When you give this, withdraw analgesics and other psychotropics and assess the patient's renal, hematologic, cardiovascular, and liver functions. The first effects appear in the form of improved sleep within several days to a week. Next, in 4 or 5 days, pain relief begins. Frequently the pain, which has previously been burning or sharp, becomes dull. Finally,

Do not use corticosteroids for long periods when your primary goal is pain relief.

ly, after 3 to 4 weeks, the patient achieves maximum pain relief.

Prescribe both these drugs with caution. You must not give amitriptyline if the patient is already on a monoamine oxidase inhibitor. First, discontinue the inhibitor and then allow a minimum of 14 days to elapse before beginning a tricyclic antidepressant such as amitriptyline. Giving both types of drugs together may result in hyperpyrexia, convulsions, and death. Amitriptyline can cause a variety of cardiovascular abnormalities and has been associated with testicular swelling and gynecomastia in men, and galactorrhea in women. It has effects like atropine; dry mouth is a common complaint.

Fluphenazine can cause cholestatic jaundice, bone marrow depression, atropine effects, and extrapyramidal syndromes. One particularly troublesome problem with fluphenazine (and other phenothiazines) is tardive dyskinesia. As the word "tardive" implies, it usually occurs after prolonged (years) therapy. The face and tongue are most commonly affected with very bizarre

and grotesque movements. Tardive dyskinesia is unresponsive to anti-parkinsonian drugs and may persist despite withdrawal of fluphenazine. It occurs more often in the elderly, in women, and in those with pre-existing brain damage. It may be heralded by fine, worm-like movements of the tongue; if you stop the drug at this stage, the condition may not develop fully.

Because of tardive dyskinesia and because the atropine-like effects of both fluphenazine and amitriptyline make the combination unacceptable to some patients, we have begun to use amitriptyline alone in the treatment of pain. Although we have done no controlled studies, preliminary results indicate that amitriptyline alone in a dosage of 50 to 100 mg at bedtime is extremely effective in a diversity of pain syndromes.

The anticonvulsants

Two anticonvulsants originally used to treat the pain of tic douloureux have also proved valuable in treating other types of burning pain associated with nerve root injury or long-standing pain believed to have a strong central nervous system component. The first is phenytoin, in a dosage of 100 mg 3 or 4 times daily. Although this drug is usually well tolerated, side effects can include bone marrow depression and central nervous system problems, such as ataxia, diplopia, and nystagmus. A pseudolymphoma with lymphadenopathy can also occur.

The second of these drugs is carbamazepine. Do not use it in the patient who has recently been on monoamine oxidase inhibitors. Nausea and vomiting (common side effects) frequently prevent the patient from taking the effective (divided) dose of 500

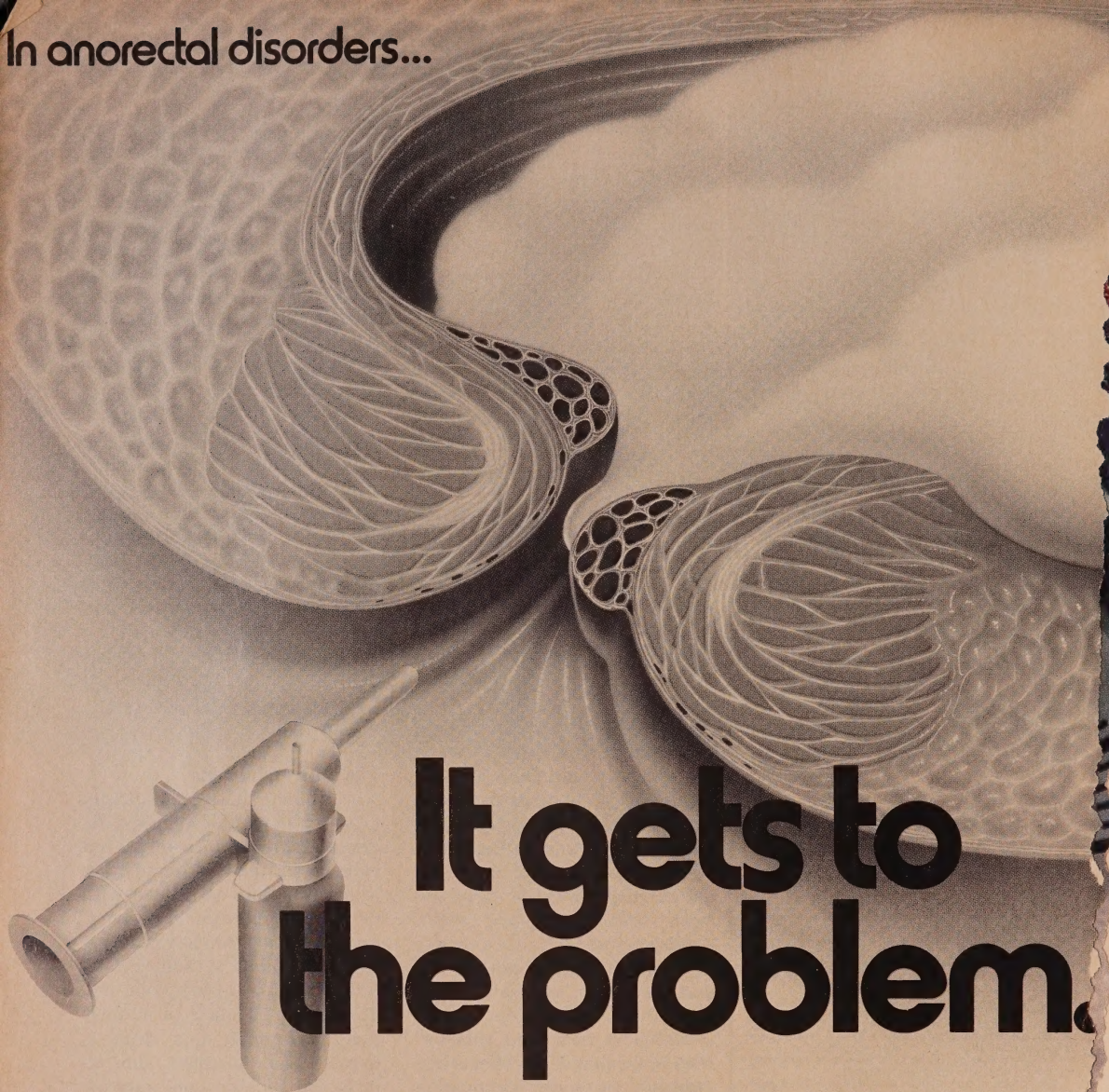
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Additional information available to the profession on request.

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In anorectal disorders...



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suppository can do.**

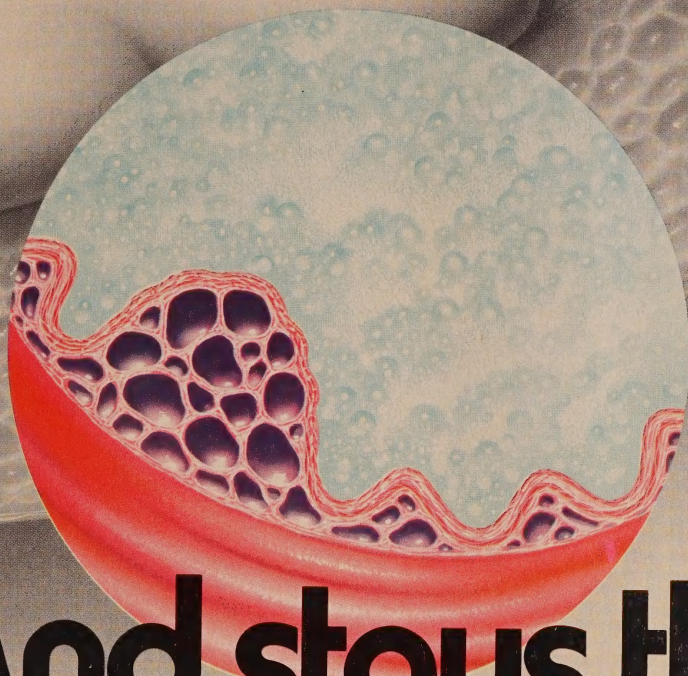
First, it fills the entire anal cavity, spreading evenly into rectal crypts, folds, papillae and hemorrhoidal sites.

Then, because it's mucoadhesive, it coats tender irritated membranes, to bring prompt, sustained and effective relief from itching and pain.

And when you prescribe Proctofoam-HC for the post-operative patient you help provide extra benefits, faster wound healing¹⁻⁴ (2½ to 3 weeks instead of 3½ to 4 weeks),⁴ less scar formation,¹⁻³ and less edema, inflammation, itching, pain and tenesmus.^{1,3-5}

proctoFoam and Proctofoam-HC are supplied with an easy-to-use, measured dose applicator which assures proper placement of the medication and prevents leaking or staining.

All this and economy too. No wonder it's the successor to the hemorrhoidal suppository.



And stays there.

Brief Summary—Proctofoam-HC

Active Ingredients: Hydrocortisone acetate 1%, and pramoxine hydrochloride 1%, in a mucoadhesive foam base.

Indications: Temporary relief of anorectal inflammation, pruritus, pain and swelling associated with hemorrhoids, proctitis, cryptitis, fissures, postoperative pain and pruritus ani.

Contraindications: Abscess, extensive fistulas or sinus tracts, tuberculosis, varicella, vaccinia or acute herpes simplex.

Precautions: A complete rectal examination to rule out serious pathology should be completed before instituting therapy. Do not use on infected lesions unless accompanied by anti-infective agents. Discontinue use if sensitivity develops.

Caution: Do not insert any part of the aerosol container into the anus. Contents of the container are under pressure, but not flammable.

Dosage: One applicatorful two or three times daily and after each bowel evacuation. Perianally, apply as needed.

How Supplied: In aerosol container providing 15 Gm. of medication (approx. 25 applications) with special rectal applicator and patient instructions.

References: 1. Bernstein, I.: *Surg. Dig.* 4:23, Jan. 1969. 2. Sladek, W. R.: Scientific Exhibit, 69th Annual Meeting of American Proctologic Society, April 1970. 3. Sladek, W. R.: *Am. J. Clin. Res.* 1:33, Jan.-Feb. 1970. 4. Miller, H.: *Am. J. Proctol.* 18:59, Feb. 1967. 5. Lieberman, W.: *Am. J. Proctol.* 20:134, April 1969.

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proctoFoam[®] and
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Each measured dose (approx. 6.5 ml.) delivers hydrocortisone acetate 1%, pramoxine hydrochloride 1%, in a water-soluble, mucoadhesive foam base.

**The successor to the hemorrhoidal suppository.
 With or without a steroid.**



Reed & Carnrick/Kenilworth, N.J. 07033

to 1000 mg daily. The drug has also been known to cause bone marrow depression and central nervous system effects. It has atropine-like properties.

The placebo effect

Most physicians think of a placebo as a sugar pill or a bolus of parenteral saline given to a patient with the suggestion that it is a pain reliever. Many physicians believe that if such an agent relieves a patient's pain, the patient is either emotionally unstable or was only faking pain in the first place. Such beliefs are naive and can only lead to less than optimal medical practice.

The placebo effect is that effect of any treatment which results from the patient's understanding of, and his emotional response to, the treatment. Since all conscious patients think and feel something when they receive any treatment, the placebo effect occurs in normal individuals and with pharmacologically active, as well as inactive, substances. The most important factor in the patient's understanding of, and emotional reaction to, a medication is what the physician conveys to him. Therefore, your instructions and attitudes can significantly alter the effect of any treatment.

Many of the specifics of the placebo response are not widely appreciated and are worth reviewing. When any new drug is tested, about 35% of patients benefit significantly from the placebo control. About 35% of anxious patients become less anxious, insomniac patients achieve sleep, and patients with pain experience pain relief when given a pharmacologically inactive agent.

There is no such thing as a typical placebo reactor. Depend-

ing on the situation, old or young, men or women, neurotic or non-neurotic respond to a placebo. The greater the patient's stress, the greater the placebo effects. Thus, placebo effects are always greater in clinical situations with sick patients than in experimental situations with nonstressed volunteers. Placebo effects are greater if the therapy is somehow perceived as more dramatic. Pills with an overpowering taste are more effective placebos than bland pills; brightly colored pills are more effective than white ones; injections are more powerful placebos than pills or capsules; and finally, new treatments have a greater placebo effect than old treatments.

Translated into practical terms, this means that the wise physician approaching the treatment of chronic pain explains his therapy with enthusiasm, and realizes that evidence of a placebo reaction is not an indication for a psychiatric consultation. Neither will he be above making minor modifications or trying new approaches to maximize the placebo effect. 

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Normoglycemia: essential in pregnant diabetic women

David J. S. Hunter, M.D.

Before insulin became available, a diabetic woman who became pregnant stood a good chance of dying of ketoacidosis, sepsis, or tuberculosis. But with insulin treatment, diabetes as a cause of maternal death soon became extremely rare.

Unfortunately, a similarly dramatic improvement did not occur among the infants born to diabetic women. Until quite recently, even in the most sophisticated hospitals with a special interest in diabetes in pregnancy, perinatal mortality was still around 10%. Compare this with an overall perinatal mortality rate of about 2%, and you can see that diabetes in pregnancy is still very hazardous to the fetus.

What happens to create this hazard? What can be done to reduce it? Let's go over the four important changes in carbohydrate metabolism during normal pregnancy and see how diabetes affects them.

In glucose tolerance

In the first trimester, glucose tolerance improves, but as the pregnancy advances, glucose tolerance gradually becomes impaired. This is probably because of insulin antagonism that follows an increase in the secretion

of the protein hormone human placental lactogen (HPL) from the syncytiotrophoblast of the placenta. This hormone, immunologically similar to growth hormone, increases fat metabolism and impairs glucose oxidation by insulin. Estrogen, a trophic hormone, increases insulin production and may be responsible for the initial improvement in glucose tolerance during the first trimester before HPL is secreted in significant quantities.

In insulin secretion

In an effort to overcome the insulin antagonism, increased quantities of insulin are secreted during pregnancy. Figure 1 shows the blood glucose and insulin levels during an oral glucose tolerance test in the pregnant and non-pregnant states. Evidently, the glucose level takes longer to peak, has a slightly higher maximum value, and takes longer to return to basal levels. During pregnancy, insulin levels reach a higher peak and also take longer to return to basal levels.

In ketone body production

The fetus uses glucose for energy and growth. To meet these needs, glucose is actively transported across the placenta. As the mother's ability to use glucose is

limited by the above factors, she mobilizes fat to provide energy when her own intake of glucose is limited. Consequently, during pregnancy ketone bodies appear in the urine after a relatively short fast. When managing diabetic patients, remember that ketone bodies in the urine do not necessarily mean ketoacidosis with hyperglycemia.

In fetal and neonatal insulin

The fetus produces insulin from its pancreatic beta cell probably as early as the 16th week of gestation. There is no transfer across the placenta of either maternal or fetal insulin. The maternal pancreas regulates maternal (therefore indirectly fetal) glucose levels so that in the normal situation, the fetal pancreas has few demands made on it before birth.

Despite active transport of glucose across the placenta, the fetal blood glucose tends to be from 20% to 50% lower than the maternal blood glucose. The fetus and newborn have a remarkable resistance to low blood glucose levels. It is not uncommon, for example, to find an infant of a diabetic mother with a neonatal blood glucose level less than 20 mg% to be totally asymptomatic. Nevertheless, it is important to prevent neonatal levels less than 20 mg% with glu-

cose administration because we now know that when a hypoglycemic infant does become symptomatic—that is, has seizures—permanent brain damage may result. On the other hand, asymptomatic hypoglycemia in newborns has no harmful neurologic sequelae, and I have seen more than one child with a blood glucose of zero before treatment who was totally asymptomatic and developed no long-term problems.

Unlike the fetus, the mother is quite sensitive to hypoglycemia and begins to develop symptoms when her blood glucose level reaches about 50 mg%. It is therefore difficult to produce profound hypoglycemia in the fetus in utero since the mother serves as an effective safety device; she becomes symptomatic long before the fetus is in trouble. What is absolutely clear, however, is that ketoacidosis is rapidly fatal for the fetus, and

pregnancies complicated by even mild ketoacidosis, if it is recurrent, have a very high still-birth rate.

How pregnancy affects diabetes

Let us now consider how these changes affect the diabetic patient during pregnancy.

The insulin requirements may be decreased during the first trimester. In fact, unexplained hypoglycemic attacks in diabetic patients may be one of the earliest signs of pregnancy. As pregnancy advances, insulin requirement increases until the time of delivery. But with delivery of the placenta, the insulin requirement decreases promptly. The patient then reverts to her pre-pregnancy insulin requirement. Patients who begin to use insulin during pregnancy usually require no further insulin after delivery.

Glucose crossing the placenta in excess quantities during maternal hyperglycemia stimulates fetal hyperinsulinemia. Under the stimulus of insulin, this glucose is deposited as fat and the fetus grows excessively large. The fetal pancreatic beta cells undergo hyperplasia under the continual stimulus of high blood glucose levels. So an infant born with beta-cell hyperplasia is likely to rapidly develop hypoglycemia after delivery. Insulin continues to pour out of the fetal beta cell but the source of glucose has been abruptly cut off with clamping of the cord so that hypoglycemia soon follows. Both these problems—overgrowth of the baby and beta-cell hyperplasia—can be avoided if maternal blood glucose levels are controlled during pregnancy.

Is pregnancy diabetogenic?

Clearly, pregnancy places excess demands on maternal mecha-

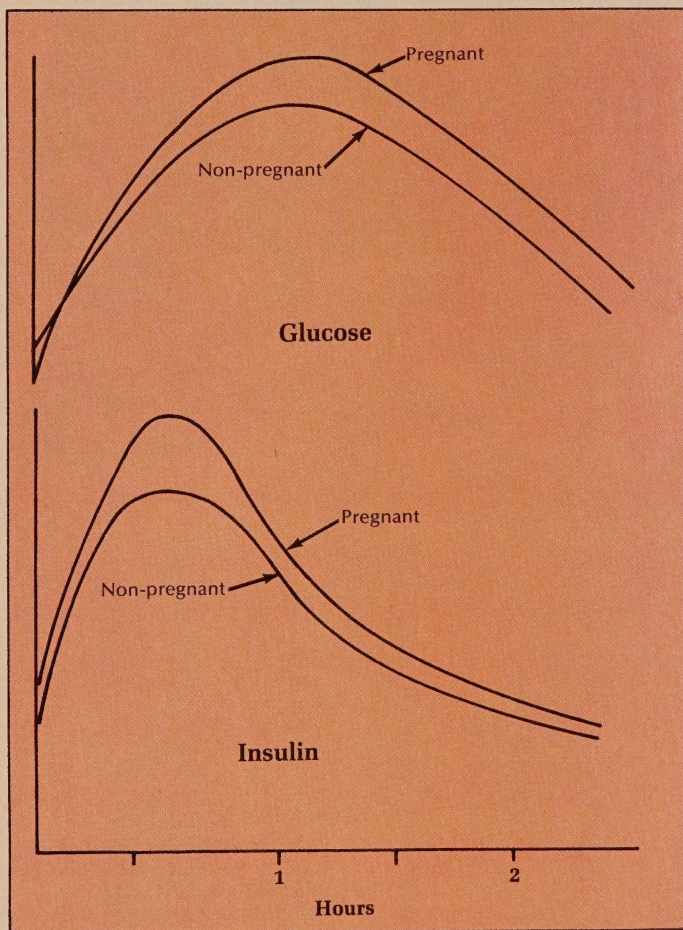


Figure 1—Glucose and insulin response during oral glucose tolerance test in pregnant and non-pregnant women.

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2 capsules STAT; followed by 1 capsule after each unformed stool, not to exceed 8 capsules/day.

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Imodium has been evaluated in more than 2,000 patients in 20 studies.

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Safe use in pregnancy has not been demonstrated.

^{††}Please see last page of advertisement for prescribing information.

for the control and symptomatic relief of
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chronic diarrhea associated with inflammatory bowel disease
...and for reducing the volume of discharge from ileostomies

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DOSAGE AND ADMINISTRATION

Acute diarrhea

The recommended initial dose of IMODIUM is two capsules (4 mg) followed by one capsule (2 mg) after each unformed stool. Daily dosage should not exceed eight capsules (16 mg). Clinical improvement is usually observed within 48 hours.

Chronic diarrhea

The recommended initial dosage of IMODIUM is two capsules (4 mg) followed by one capsule (2 mg) after each unformed stool until diarrhea is controlled, after which the dosage of IMODIUM should be reduced to meet individual requirements. When the optimal daily dosage has thus been established, this amount should then be administered as a single dose or in divided doses.

The average daily maintenance dosage in clinical trials was two to four capsules (4-8 mg). A dosage of eight capsules (16 mg) was rarely exceeded. If clinical improvement is not observed after treatment with eight capsules (16 mg) of IMODIUM per day for at least 10 days, symptoms are unlikely to be controlled by further administration. IMODIUM administration may be continued if diarrhea cannot be adequately controlled with diet or specific treatment.

new IMODIUM[®] CAPSULES
(loperamide HCl)

Brief Summary: Before prescribing, please consult complete prescribing information, a summary of which follows:

DESCRIPTION: IMODIUM (loperamide hydrochloride), 4-(p-chlorophenyl)-4-hydroxy-N,N-dimethyl- α , α -diphenyl-1-piperidinebutyramide monohydrochloride, is a synthetic antidiarrheal for oral use.

IMODIUM capsules are classified as a Schedule V controlled substance by federal law (see: Overdosage Section).

CONTRAINDICATIONS: IMODIUM is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS: Antiperistaltic agents should not be used in acute diarrhea associated with organisms that penetrate the intestinal mucosa, e.g., toxigenic *E. coli*, *Salmonella*, *Shigella*, and in pseudomembranous colitis associated with broad-spectrum antibiotics.

Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of IMODIUM does not preclude the administration of appropriate fluid and electrolyte therapy. In some patients with acute ulcerative colitis, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. IMODIUM therapy should be discontinued promptly if abdominal distention occurs or if other untoward symptoms develop in patients with acute ulcerative colitis.

PRECAUTIONS: In acute diarrhea, if clinical improvement is not observed in 48 hours, the administration of IMODIUM should be discontinued.

Abuse and Dependence: Physical dependence to IMODIUM in humans has not been observed. However, studies in monkeys demonstrated that loperamide hydrochloride at high doses produced symptoms of physical dependence of the morphine type.

Carcinogenesis: In an 18-month rat study with doses up to 133 times the maximum human dose (on a mg/kg basis) there was no evidence of carcinogenesis.

Pregnancy: Safe use of IMODIUM during pregnancy has not been established. Reproduction studies performed in rats and rabbits with dosage levels up to 30 times the human therapeutic dose did not demonstrate evidence of impaired fertility or harm to the offspring due to IMODIUM. Higher doses impaired maternal and neonate survival, but no dose level up to 30 times the human dose demonstrated teratogenicity. Such experience cannot exclude the possibility of damage to the fetus. IMODIUM should be used in pregnant women only when clearly needed.

Nursing Mothers: It is not known whether IMODIUM is excreted in human milk. As a general rule, nursing should not be undertaken while a patient is on a drug since many drugs are excreted in human milk.

Pediatric Use: Safety and effectiveness in children have not been established.

Therefore, use of IMODIUM is not recommended in the pediatric age group (under the age of 12). In case of accidental ingestion of IMODIUM by children, see Overdosage Section for suggested treatment.

ADVERSE REACTIONS: The adverse effects reported during clinical investigations of IMODIUM are difficult to distinguish from symptoms associated with the diarrheal syndrome. Adverse experiences recorded during clinical studies with IMODIUM were generally of a minor and self-limiting nature. They were more commonly observed during the treatment of chronic diarrhea.

The following patient complaints were reported:

Abdominal pain,	Dry mouth
distention or discomfort	Nausea and vomiting
Constipation	Skin rash
Drowsiness or dizziness	Tiredness

OVERDOSAGE: Animal pharmacological and toxicological data indicate that overdosage in man may result in constipation, CNS depression, and gastrointestinal irritation. In clinical trials an adult who took three 20 mg doses within a 24-hour period was nauseated after the second dose and vomited after the third dose. If vomiting has occurred spontaneously, a slurry of 100 gm of activated charcoal should be administered orally as soon as fluids can be retained.

If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 gm of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone. In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Based on the fact that relatively little drug is excreted in urine, forced diuresis is not expected to be effective for IMODIUM overdosage.

HOW SUPPLIED: IMODIUM is available as 2 mg capsules of loperamide hydrochloride. The capsules have a light green body and a dark green cap, with "ORTHO 1000" imprinted on each segment. IMODIUM capsules are supplied in bottles of 100.

IMODIUM (loperamide hydrochloride) is an original product of Janssen Pharmaceutica, Belgium, and co-developed by Ortho Pharmaceutical Corporation.

U.S. Patent 3,714,159

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869



ORJ 430-SR

nisms involved in controlling blood glucose. So it is not surprising that in some patients, pregnancy brings to light defects in the glucose handling system. (Figure 2 graphically demonstrates the demands imposed by pregnancy and how, if they are not met, the patient will become diabetic.) The important point, however, is that the patient's problem lasts only as long as the pregnancy and after this "stress event" the patient is, in most cases, normal. Patients who need insulin to control blood glucose only during pregnancy have "gestational diabetes." Between pregnancies, they are in a latent phase and therefore have "latent diabetes."

In some patients, the only demonstrable abnormality is an abnormal glucose tolerance test. The patient can maintain a normal blood glucose level during the day on a normal calorie intake. Those patients have "chemical diabetes"; their abnormality shows only upon chemical testing. If their abnormality is present only during the pregnancy, they have "chemical gestational diabetes."

Glucose tolerance tests

Tolerance to a glucose load may be measured by giving intravenous or oral glucose. Intravenous testing is tedious and requires multiple blood sampling and, in terms of screening the population for problems that require treatment, it offers nothing over the simpler, more acceptable oral glucose tolerance test.

An abnormality of carbohydrate tolerance in pregnancy, if missed, is probably associated with a fetal loss rate equal to that in a patient with established diabetes. To prevent this, it is essential to look carefully for diabetes in obstetric patients. The follow-

ing conditions call for a glucose tolerance test during pregnancy:

- Family history of diabetes
- History of a previous stillbirth
- Maternal age over 35
- Fasting glycosuria
- History of a previous large baby
- Appearance of hydramnios
- Abnormal glucose tolerance test in previous pregnancy.

The most important index in evaluating the abnormal glucose tolerance test is the fasting blood glucose level. If this is over 100 mg%, the patient is unlikely to be able to control her blood glucose within the normal range throughout the day (between 65 and 120 mg%). The next most important point is the 2-hour postprandial glucose level which should have returned to within 20 mg of the fasting level.

If the fasting glucose is normal and the 2-hour postprandial glu-

cose is normal but the half- and one-hour values are high, the patient probably can maintain normoglycemia throughout the day. Whether or not she needs insulin can only be determined by studying the 2-hour postprandial blood sugar levels over a 24-hour period.

First, restrict such a patient to an 1,800-calorie diet that contains 180 grams of carbohydrate. After she has followed this diet for at least 3 days, estimate the blood glucose fasting and 2 hours after breakfast, lunch, and supper. If you find any value over 120 mg% while the patient is on an 1,800-calorie diabetic diet, the patient should probably be started on insulin.

Perinatal mortality

It has taken nearly 20 years to accept the idea that the outcome of pregnancy in a diabetic pa-

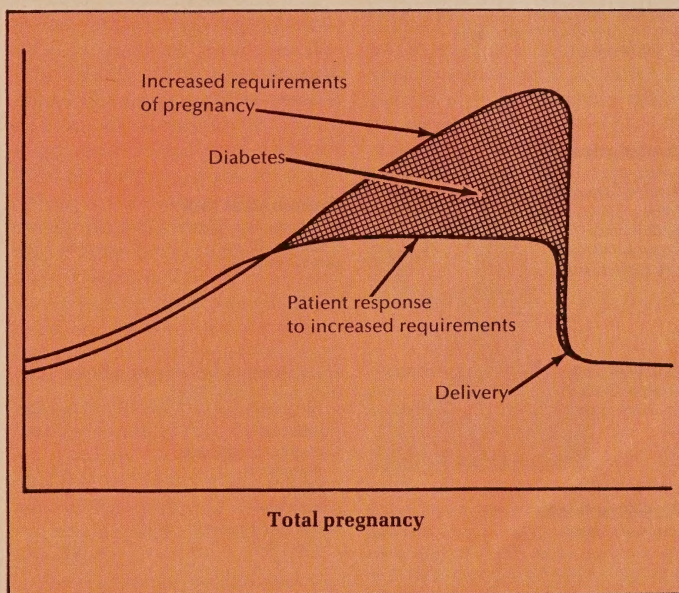


Figure 2—Failure to meet increased demands on carbohydrate homeostatic mechanisms during pregnancy results in diabetes, which disappears promptly with delivery of the placenta.

THERAPEUTIC INDEX

Analgesics

Bayer Aspirin/Glenbrook 130
 Darvon Compound-65/Lilly 14-15
 Empracet w/Codeine No. 4/
 Burroughs Wellcome 2
 Fiorinal/Sandoz fourth cover
 Percodan/Endo 53

Antacids

Dicarbosil/Arch 16
 Riopan/Ayerst 52

Antiarthritics

Naprosyn/Syntex 146-148

Antiasthmatics

Vanceril/Schering 38-40

Antibacterials/Antiseptics

Bactrim DS/Roche 113-114
 Macroclantin/Eaton 92-93
 Septra, Septra DS/Burroughs
 Wellcome 22

Antibiotics

Achromycin V/Lederle .. second cover
 Amoxil/Beecham 54-55
 Keflex/Lilly 156-157
 Kefzol/Lilly 86-87
 Tegopen/Bristol 118-119
 Vibramycin/Pfizer 67-68

Antidepressants/Tranquilizers

Etrafon/Schering 6-8
 Pamelor/Sandoz 95-96

Antidiarrheals

Imodium/Ortho 164-166

Antiflatulants

Mylcon-80/Stuart Pharmaceuticals,
 Division of ICI,
 United States Inc. 161

Antihistamines

Dimetapp Extentabs/Robins 20-21

Anti-inflammatory Agents

Proctofoam, Proctofoam-HC/
 Reed & Carnrick 158-159

Antinauseants

Bendectin/Merrell 50-51

Antipruritics

Atarax/Roerig 58-59

Antispasmodics/ Anticholinergics

Bentyl/Merrell 18-19
 Librax/Roche 76-78

Ataractics

Miltown/Wallace 69

Bronchodilators

Aminophyllin/Searle 70-71
 Brethine/Geigy 143-144
 Marax/Roerig 4-5

Cardiovascular Preparations

Aldomet/Merck Sharp
 & Dohme 80-84
 Arlidin/USV 128
 Catapres/Boehringer
 Ingelheim 28-30
 Inderal/Ayerst 150-154
 Isordil/Ives 72
 Nicobid/Armour
 (free Rx) 137-138

Contraceptives

Cu-7, Mark-7/Searle 10-11
 Ovcon-35/Mead Johnson 120-122

Cough & Cold Preparations

Novafed/Dow 172-third cover
 Organidin/Wallace 44-45
 Robitussin-DM/Robins 74

Decongestants/Expectorants

Afrin/Schering 17
 Dimetane Expectorant-DC/
 Robins 124-125

Diagnostics

N-Multistix/Ames 46-47

Diuretics

Aldactazide/Searle 90-91
 Dyazide/Smith Kline
 & French 12
 Hygroton/USV 106-107

Educational Services

Institutional/Ayerst 170-171
 Institutional/Roche 98

H₂ Antagonist

Tagamet/Smith Kline &
 French 33-36

Hormones

Estrace/Mead Johnson 102-104

Laxatives

Doxidan/Hoechst-Roussel 108
 Metamucil/Searle 63
 Peri-Colace/Mead Johnson 101
 Senokot/Purdue Frederick 116

Parasympatholytic Agents

Bellergal-S/Dorsey 88-89

Thyroid Preparations

Synthroid/Flint 49

tient depends fundamentally on how well the blood glucose level has been controlled throughout pregnancy. The problem has not been to establish that some control of blood glucose is essential, but to accept the idea that *anything short of normoglycemia is sub-optimal*. Clearly it requires extraordinary, indeed obsessive, dedication to assure that every pregnant diabetic patient has a blood glucose that never exceeds 120 mg%. But reports now coming from centers that try to practice this philosophy show perinatal mortality rates that are equal to those for the population at large.

Urinalysis variable

Unfortunately, due to the change in renal threshold for glucose during pregnancy, the urine glucose levels bear an inconstant relation to blood glucose levels. Urinalysis therefore cannot be used for tight control of blood glucose levels. Instead, the best guide for control is the 2-hour postprandial glucose level after each meal, since this is likely to be the time when blood glucose is at its highest. At the West Virginia University Medical Center, pregnant diabetic patients are routinely hospitalized for a 24-hour blood glucose profile to accompany each antenatal visit. These visits are usually scheduled every 3 weeks to the 24th week, every 2 weeks to the 30th week, and after that weekly until the time of delivery. Delivery is usually undertaken at 38 weeks' gestation. An amniocentesis for lecithin/sphingomyelin (L/S) ratio always precedes delivery to check that the infant will not develop hyaline membrane disease.

Patients with mild abnormalities of glucose tolerance who do not require insulin are controlled

on an outpatient basis with "random" glucose estimation at each visit. These patients are usually delivered at term.

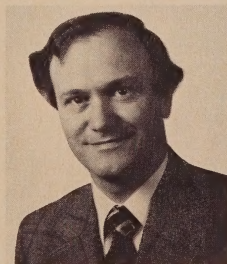
What kind of insulin?

A combination of NPH and regular insulin, twice a day if necessary, usually proves most satisfactory. The fasting glucose level is controlled essentially by the evening NPH; the post-breakfast by the morning regular; the post-lunch by the morning NPH; and the post-supper by the afternoon regular insulin. Three snacks between meals help to even out the calorie intake throughout the day.

Not to give credit to other advances in perinatology that have occurred in the last 5 to 10 years would be unfair. Some such improvements are the management of hyaline membrane disease, the increasing availability of well-staffed and well-equipped neonatal units, the development of the lecithin/sphingomyelin ratio in amniotic fluid and its relationship to hyaline membrane disease in the newborn, and the development of ultrasound and its use in obstetrics. The fact remains, however, that patients who have been well controlled throughout pregnancy may be expected to deliver a mature fetus that is not above average birth weight and does not develop troublesome hypoglycemia or respiratory distress. Although these babies still need careful watching over the first few hours of their lives, they are unlikely to develop severe neonatal problems if the maternal blood glucose has been controlled accurately throughout the pregnancy.

The incidence of diabetes in pregnancy runs at around 1% of all pregnancies. Thus, the average physician who practices

obstetrics can expect to see about two diabetic patients a year. Therefore, if he sees only one stillbirth in 5 years, his mortality rate would be unacceptably high. The individual physician cannot be expected to maintain the facilities required for adequate care of the pregnant diabetic patient; only the teamwork, facilities, and staff expertise in a large hospital that sees many such patients a year can best look after diabetic problems in pregnancy. To make such care accessible to every patient who needs it, pathways of referral for such patients are being organized all over the country in "Regionalization of Perinatal Care" programs. There can be little excuse any longer for late referrals of such patients for specialized care. The days of "salvage situations" for pregnant diabetic patients should be over. To get this care, patients must accept that in many situations they will frequently have to travel long distances and spend considerable time in the hospital undergoing control of their diabetes. When the advantages are carefully explained in detail, most patients



Dr. Hunter is associate professor in the department of obstetrics and gynecology, West Virginia University Medical Center, Morgantown, West Virginia, and director of fetal maternal medicine. He is a member of the Royal College of Obstetricians and Gynaecologists of England and a fellow of the American College of Obstetricians and Gynecologists.

New Horizons in Hyperlipidemia

THE LIPID- LADEN CELL

VLDL

LDL

HDL

Medical artist's interpretation of arterial smooth muscle cell interacting with lipoproteins.

Make sure about new antibiotics

John G. Bartlett, M.D.

Selecting a new antibiotic is not easy. Even after it wins FDA approval, the new agent's side effects and cost-to-benefit ratio will not become apparent until several years after its introduction.

How do you know whether a new antibiotic is better than older antibiotics or whether its side effects are worse than those of already established antibiotics? The answer is, you do not—at least not always. Let's review the newer antibiotics and compare them with older drugs to see what to expect.

Keeping side effects down

An important consideration in selecting a drug is its side effects. The best way to avoid unnecessary side effects is not to prescribe an antibiotic when it is not indicated. Studies show that most antibiotics are ordered not for bacterial infections, but for viral illnesses, for prophylaxis after surgery, or for use as needed by the patient. In such cases a patient runs just as high a risk of side effects as he does when

he really needs the drug. Antibiotic overuse can also make treating a bacterial infection more difficult.

The incidence of gram-negative bacteremia increased from less than one patient per 1,000 hospital admissions in the days before antibiotics to 10 patients per 1,000 in the 1970s. Many authorities believe that excessive antimicrobial use is largely responsible for this trend.

Cost: something to consider

Cost of a drug is not a consideration when the patient has a life-threatening infection; however, it is important when the infection is not serious. When several drugs are equally effective, the one that costs the least and has the fewest side effects is often the agent of choice. This is why some of the older antimicrobials, such as sulfa, tetracycline, and ampicillin, are preferred for most community-acquired urinary tract infections.

AMOXICILLIN

Amoxicillin is a new aminopenicillin with a spectrum of

activity similar to that of ampicillin. The drug is usually effective against streptococci (including enterococci), *Haemophilus influenzae*, *Neisseria*, *Salmonella*, and community-acquired strains of *Escherichia coli* and *Proteus mirabilis*. Many organisms are resistant to amoxicillin. Among the resistant organisms are *Staphylococcus aureus*, *Klebsiella*, *Serratia*, indole-positive *Proteus*, and *Pseudomonas aeruginosa*.

Advantages over ampicillin

Amoxicillin is absorbed better than ampicillin; an oral dose will give twice as high a blood level as the same dose of ampicillin. The side effects of amoxicillin are generally similar to those of ampicillin. Because of better absorption, amoxicillin may cause less diarrhea than ampicillin—though this is not known for sure. It is also not known whether amoxicillin is responsible for the rash that is commonly observed with ampicillin and thought to be unrelated to hypersensitivity.

By itself, a 3-gm dose of amoxicillin is as effective in gonorrhea

as is 3.5 gm of ampicillin given along with 1 gm of probenecid. Amoxicillin is also better than ampicillin in the oral treatment of salmonellosis. Do not use it to treat shigellosis, since trials have shown that ampicillin is a better drug for treating bacillary dysentery.

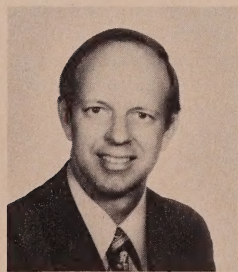
Amoxicillin is more expensive than ampicillin, but a given dose of it provides a higher blood level than ampicillin. If this permits halving the dosage of amoxicillin, the two agents may be more competitively priced. Amoxicillin may eventually supplant ampicillin in the treatment of urinary tract infections, otitis media in children, and exacerbations of chronic bronchitis. However, this will not be known until additional data are available, particularly regarding the incidence of side effects.

CEPHALOSPORINS

Cephalosporins differ in their rate of absorption and in their side effects but most have a similar antibacterial action.

Oral form: overused

Oral cephalosporins are among the most overused of antibiotics.



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Cephalexin and cephadrine are about the same in oral absorption and other respects. The main problem is that they are often prescribed to treat a mild infection when a much less expensive antimicrobial would do. A clear indication for cephalexin or cephadrine is a *Klebsiella* urinary tract infection when the oral treatment is appropriate.

Parenteral forms

Cephalothin, cephalirin, and cephadrine are short-acting drugs: each has a half-life of about 30 to 40 minutes, and provides a peak blood level of 10 to 20 $\mu\text{g/ml}$ following a 500-mg intramuscular dose. The three drugs are equal in cost and other aspects.

Cephaloridine and cefazolin are the long-acting cephalosporins. Each has a half-life of 80 to 110 minutes, which means they can be given less often than short-acting forms of the drug. Cefazolin has several potential advantages over other parenteral cephalosporins. It produces very high peak blood levels ($> 70 \mu\text{g/ml}$ following an intramuscular dose of 500 mg); high bile levels; longer half-life; and, compared with cephaloridine, less nephrotoxicity. Injection of cefazolin causes very little pain—a clear improvement over cephalothin. The advantage of high blood levels achieved with cefazolin may be somewhat offset by the higher serum protein binding.

Current state

In summary, there are four things that can be said about cephalosporins:

1. With the exception of a *Klebsiella* urinary tract infection, most mild or moderate infections can be treated just as well—and less expensively—with a drug other than oral cephalosporins.

2. Cefazolin is the intramuscular cephalosporin of choice.

3. The nephrotoxicity it causes may mean that cephaloridine is no longer indicated in the treatment of any infection.

4. Cefazolin, cephalothin, cephalirin, and cephadrine are about equal for intravenous use, providing the drug is given in the right dosage at appropriate intervals.

TETRACYCLINES

More than 3,000 tetracyclines have been developed (compared with 20,000 penicillins and 7,000 cephalosporins), but only a tiny fraction of these have reached the market. Two new and useful tetracyclines are doxycycline and minocycline.

Advantages

Because each drug has a longer half-life than ordinary tetracycline, doxycycline and minocycline can be given twice daily. Doxycycline has another advantage: it is not excreted in the urine, so it can be used in the usual dosage in renal failure.

Spectrum of action

Minocycline is better than other tetracyclines against *Staphylococcus aureus*, but it is seldom regarded as a preferred agent in staphylococcal infections. Minocycline and doxycycline are more effective against anaerobic bacteria such as *Bacteroides fragilis*. However, since a third of *B. fragilis* strains are resistant to doxycycline and minocycline, do not use these drugs as first line therapy for a serious *B. fragilis* infection unless in vitro susceptibility tests show efficacy.

Current state

Cost is a consideration in choosing minocycline or doxycycline

because ordinary tetracycline is less expensive and equally effective against many infections. Doxycycline is indicated in certain instances:

- It is the tetracycline of choice for a patient with kidney failure.
- It can be given twice a day. That makes it useful when a patient is unlikely to take medicine 4 times a day.
- If subsequent studies show that intravenous doxycycline causes less thrombophlebitis, that would be another advantage over the parent compound.

Minocycline is no longer so useful as it was for exposure to meningococcal meningitis. The drug causes vertigo in a large number of people who take it. Refusal of persons who experience vertigo to continue taking the drug has deterred many authorities from recommending it in meningitis prophylaxis.

TRIMETHOPRIM-SULFA

Trimethoprim and sulfamethoxazole are synergistic, and this combination is useful in urinary tract and other infections.

Urinary tract infections

Chronic prostatitis can be difficult to eradicate. For some men it becomes a nagging problem and a cause of recurrent urinary tract infections. Trimethoprim can eliminate the prostatic residue of bacteria in these patients. The dosage usually recommended is two tablets twice a day for 12 weeks.

Another form of urinary tract infection in which trimethoprim-sulfa has shown promise is in the prevention of recurrent cystitis in women. Half a tablet daily was more effective than other antimicrobials in preventing infections. Once-daily dosing is an added benefit in terms of com-

pliance. The combination can help in other urinary tract infections, but should not be used until less expensive drugs have failed.

Trimethoprim-sulfa is effective in the treatment of typhoid fever. In occasional patients the drug has produced a dramatic

"When several drugs are equally effective, the one that costs the least and has the fewest side effects is often the agent of choice."

cure after the patient failed to respond to chloramphenicol.

The drug combination has been approved for the treatment of pneumonia due to *Pneumocystis carinii*. Trimethoprim-sulfa and pentamidine appear to be equally effective, but trimethoprim-sulfa is far less toxic.

AMINOGLYCOSIDES

Gentamicin is usually regarded as the drug of choice for treating serious gram-negative sepsis before the cultures are back. Two new aminoglycosides are tobramycin and amikacin.

Tobramycin

Tobramycin's spectrum of activity is similar to that of gentamicin, though it is more effective than gentamicin against *P. aeruginosa*. The dosage and side effects of tobramycin and gentamicin are identical. The main question, then, is whether its effectiveness against *Pseudomonas* makes tobramycin preferable to gentamicin for routine use. Most infectious disease authorities think not. The only time they recommend tobramycin is when susceptibility

tests show that it is superior to gentamicin.

Amikacin

A big plus for amikacin is that it is usually effective against gram-negative bacilli that are resistant to gentamicin. Also, higher blood levels of amikacin can be achieved: 20 to 30 $\mu\text{g/ml}$ compared with 4 to 8 $\mu\text{g/ml}$ for gentamicin or tobramycin. Nevertheless, clinical studies indicate that these three agents are equally effective in treating susceptible pathogens providing proper doses are used. Like other aminoglycosides, amikacin can cause nephrotoxicity and ototoxicity. The relative rates of ototoxicity and nephrotoxicity for gentamicin, tobramycin, and amikacin are not yet known, but available data suggest that they are similar.



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Warts: how to tell them apart and what to do about them

Arthur B. Kern, M.D.

Fortunately many warts involute spontaneously within 2 years and need little, if any, attention. Still they are a nuisance, they can be unsightly, they can be painful, and most people want to be rid of them quickly. To help patients do that you must be able to distinguish warts and be able to treat them correctly. Here's how to go about that.

The wart-causing papovavirus belongs to the DNA virus group, probably the most important of all the viruses causing skin lesions. Warts come in many varieties.

1. The common wart

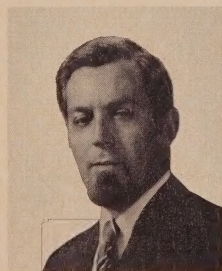
The elevated, firm papule you most often see on the fingers and dorsa of the hands is the common wart. It can also occur periungually or subungually. It varies from flesh tone to light brown in color and can be large, small, single, or multiple. Once in a while you see the elongated protuberances called filiform warts.

Usually asymptomatic, the common wart can be tender, especially if it is fissured or growing on the palmar surface of the finger. Warts rarely occur in early childhood, and become more common during the school years, then decrease in frequency. They can usually be diagnosed easily from their clinical features. If they do not clearly fit the description, the differential diagnosis should include actinic keratosis, basal cell and squamous cell cancer, melanoma, and pigmented nevus. If in doubt, do a biopsy and histopathologic examination before beginning treatment.

Traumatic destructive and mutilating treatment has no place in the therapy for young children. Be sure not to let the child's parents pressure you into that kind of treatment. Always try simple, conservative measures first. It may help if you acquaint the parents with the natural history of warts and reassure them about the likelihood of their disappearance—often without treatment.

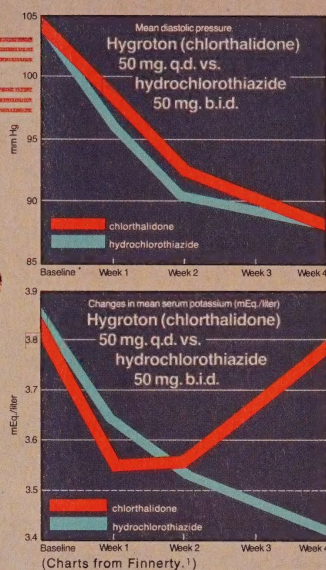
If treatment is indicated, first try applying bichloroacetic acid at 2- to 4-week intervals. During that time a mixture of acids in flexible collodion, such as Duo-film, should be applied once a day. That should do the job.

Curettage and electrosurgery (under lidocaine anesthesia) should be reserved for older patients with greater pain tolerance who have only a few warts. Re-



Dr. Kern is clinical associate professor of medicine (subsection of dermatology) at Brown University and director of the dermatology department at Miriam Hospital, Providence, Rhode Island. He is a fellow of the American Academy of Dermatology and a member of the Society for Investigative Dermatology.

New double-blind study In hypertension... Hygroton (chlorthalidone) vs. hydrochlorothiazide



Hygroton achieves

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Frank A. Finnerty, Jr.¹

Hygroton® (chlorthalidone) 50 mg. blocks sodium retention longer

BRIEF SUMMARY

Indications: Hypertension, adjunctive therapy in edema. **Contraindications:** Anuria, hypersensitivity to chlorthalidone or other sulfonamide-derived drugs.

Warnings: Should be used with caution in severe renal disease, impaired hepatic function or progressive liver disease. May add to or potentiate the action of other antihypertensive drugs. Sensitivity reactions may occur in patients with a history of allergy or bronchial asthma. Thiazides cross the placental barrier and appear in cord blood. Use in pregnant women requires that the anticipated benefits of the drug be weighed against possible hazards to the fetus. These hazards include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. In nursing mothers, thiazides cross the placental barrier and appear in breast milk. If use of the drug is essential, the patient should stop nursing.

Precautions: Periodic determination of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals. All patients receiving chlorthalidone should be observed for clinical signs of fluid or electrolyte imbalance; namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Hypokalemia may develop with chlorthalidone as with any other potent diuretic, especially with brisk diuresis, when severe cirrhosis is present, or during concomitant use of corticosteroids or ACTH. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Digitalis therapy may exaggerate metabolic effects of hypokalemia especially with reference to myocardial activity. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather. Hyperuricemia may occur or gout be precipitated in certain patients. Insulin requirements in diabetic patients may be increased,

decreased, or unchanged and latent diabetes mellitus may become manifest. Chlorthalidone and related drugs may increase the responsiveness to tubocurarine. The antihypertensive effects of the drug may be enhanced in the postsympathectomy patient. Chlorthalidone and related drugs may decrease arterial responsiveness to norepinephrine. If progressive renal impairment becomes evident, as indicated by a rising nonprotein nitrogen or blood urea nitrogen, a careful reappraisal of therapy is necessary with consideration given to withholding or discontinuing diuretic therapy. Chlorthalidone and related drugs may decrease serum PBI levels without signs of thyroid disturbance. **Adverse Reactions:** Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, dizziness, vertigo, paresthesias, headache, xanthopsia; leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia; purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), Lyell's syndrome (toxic epidermal necrolysis). Orthostatic hypotension may occur and may be aggravated by alcohol, barbiturates or narcotics. Other adverse reactions include hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, impotence. Whenever adverse reactions are moderate or severe, chlorthalidone dosage should be reduced or therapy withdrawn. **Usual Dose:** One tablet daily. **How Supplied:** Tablets—100 mg. (white, scored) and 50 mg. (aqua) in bottles of 100 and 1000; PAKs of 28 tablets, boxes of 6.

Reference: 1. Finnerty, F. A., Jr.: Hypertension: The Continuing Challenge, Scientific Exhibit, Meeting of AAFP, Boston, Mass., Sept. 20-23, 1976.

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member, however, that this method on the palmar surface of the distal phalanx may result in a tender scar. Also, curettage and electrosurgery on periungual warts can cause trouble by damaging the nail matrix, resulting in deformity. Surgical excision is generally contraindicated for the common wart, both because warts do recur and because it is apt to leave tender scars.

2. The flat (juvenile) wart

As a rule, flat warts are smaller than common warts, usually measuring only 2 to 3 mm across. They are smooth, flesh-colored, and generally occur on the face and the dorsa of the hands, in groups ranging in number from just a few to hundreds. They are usually asymptomatic. Most common in young children, they decrease in frequency with age. The juvenile wart has a distinctive appearance, but at times can be confused with an acne papule or closed comedo. If in doubt, again, biopsy.

You need a peeling agent to treat flat warts. A solution of retinoic acid or 5% or 10% benzoyl peroxide, applied once or twice daily for up to 6 months, is usually adequate to peel off the warts. In unusually persistent cases, and only as a last resort, use liquid nitrogen or electrosurgery. Remember though that both are painful and cause scarring.

3. The planar wart

As its name indicates, the planar wart is found on the planar surface of the foot. This wart can be asymptomatic or, if located in a weight-bearing area, extremely painful. The patient commonly complains of the sensation of a pebble in his shoe. It is most common in school-aged children; its

spread appears to be related to going barefoot in showers, locker rooms and, of course, swimming pools. Like all warts, it can be single or multiple. Occasionally, you see a mosaic planar wart, a composite of many small warts in a limited area, arranged in a mosaic pattern. All of them are usually darker than normal skin.

Planar warts are easily confused with callosities. To make the differentiation, pare them down slightly. On the planar wart you see small black dots representing capillary tips, and interruption of the normal lines of the skin at the sharply demarcated edge of the wart.

Treatment varies widely. Almost everyone has a favorite

Traumatic destructive and mutilating treatment has no place in the therapy for young children. Always try simple, conservative measures first. It may help to reassure parents about the likelihood that warts will disappear—often without treatment.

treatment for planar warts. If the lesion is single, I prefer to apply cantharidin after surgical paring. I cover this with a layer of plastic tape and a second layer of adhesive tape. I instruct the patient to leave the tape in place for 7 days and to keep the foot dry. He then removes the tapes and soaks his foot for 30 minutes daily in lukewarm water.

Cantharidin works by causing a blister. The resulting reaction lifts out the wart. Be sure to warn your patient that the reaction may cause considerable pain. If it does, he should remove the tapes and start the soaks earlier. One treatment may be enough, or if not, repeat it several times, at 2-week intervals, if necessary.

For multiple lesions, or when

both feet are affected, I do not recommend cantharidin because it is too irritating. In such cases I use one of the following two methods.

In the first, I apply a mixture of 50% podophyllin and 25% salicylic acid in tincture of benzoin (after surgical paring). I then cover each lesion with a piece of 40% salicylic acid plaster cut slightly smaller than the wart, and secure it with adhesive tape. The patient may replace the plaster whenever it comes off and he need not keep his feet dry. Like cantharidin, podophyllin can cause a strong local reaction, so be sure to advise the patient to remove the plaster if he suffers any appreciable discomfort. I follow these patients at 2-week

intervals and re-treat if necessary.

The second method is especially useful if the patient has a great many warts. I instruct him to soak the affected areas in a solution of formaldehyde for 20 minutes each day, mixing 2 parts of water to 1 part 10% formaldehyde. I pare the lesions at 2-week intervals. If response is not adequate within 4 weeks, I increase the strength of the solution by mixing equal parts of water and formaldehyde. (Be sure to tell the patient to cover surrounding areas with Vaseline before soaking, to protect normal skin.) Allergic sensitivity to formaldehyde—redness, irritation, or itching—requires immediate cessation of treatment.

If conservative therapy fails

to cure an asymptomatic or minimally painful lesion, I usually advise the patient to try to learn to live with it. I use curettage and electrosurgery only if the wart has not responded to a long trial of more conservative measures and is still painful. I use surgery only in the most extreme cases, for it too often results in scars that are more painful than the original wart. I use radiation therapy only rarely. If it must be done, it should be done by a physician properly trained in this therapy and conversant with its hazards.

4. Venereal warts

Venereal warts, more properly called condylomata acuminata, occur on the genitalia and in the perianal region. They are generally related to sexual activity, and usually occur in adults only. They are typically whitish to light brown in color, and can be small and few in number. If untreated, they can become massive and numerous. Associated symptoms may occur with them.

Condylomata acuminata must be distinguished from condylomata of secondary syphilis and from squamous cell cancer. In syphilis, the lesions tend to be smaller and, most important, to be associated with lesions in other areas, such as papules in the perioral area, on the trunk, arms, and legs, and with mucous patches in the mouth. To confirm the diagnosis, use dark-field examination and serologic tests for syphilis. If you suspect epidermoid cancer, you should biopsy the tissue.

Most venereal warts respond quickly to weekly applications of a 25% solution of podophyllin in tincture of benzoin. *It must always be administered by the physician.* Apply it with care and, initially, in limited amounts

because of the risk of a severe, sometimes violent reaction. Be sure to instruct the patient to bathe or shower 5 hours after the application to remove the medication.

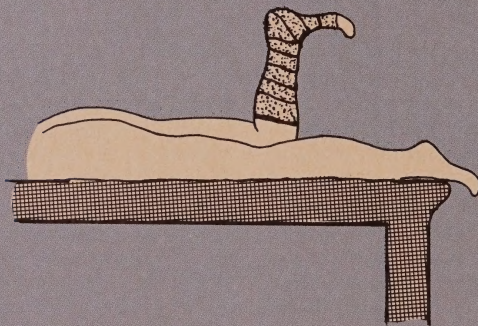
If the lesions have not involuted after 3 or 4 treatments, use a stronger solution of 50% podophyllin and 25% salicylic acid in tincture of benzoin. A lack of response of perianal

condylomata may be due to reinfection from intrarectal lesions. In such cases, the intrarectal lesions should be surgically removed. Another cause of treatment failure is reinfection by the sexual partner. If you have ruled out this possibility and the lesion still persists, you may have to resort to destructive treatment with liquid nitrogen or electrosurgery. ✎



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—Sam Lerman, M.D.
Southfield, Mich.

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These are the patients who can benefit from the *high antifatulent capacity of Mylicon®-80*. It promptly and effectively relieves the gaseous symptoms of aerophagia.

And Mylicon-80 is safe...even as concomitant therapy.

MYLICON®-80

(simethicone-80 mg.)

HIGH CAPACITY ANTIFLATULENT

Usual dosage: One tablet four times daily after meals and at bedtime, or as directed by a physician. Tablets should be chewed thoroughly.



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Estradiol...the only estrogen necessary in estrogen replacement therapy

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Estradiol, the active estrogen at the cellular level

Estradiol is the primary estrogen of the human ovary—estrone and estriol are considered its oxygenated metabolites¹—and the major estrogen secreted during the reproductive life of the woman.²

Estradiol, not estrone, is the logical estrogen to replace

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Estradiol was long thought desirable in oral estrogen replacement therapy, but administration was not practical owing to erratic absorption. With the technique of micronization, dependable oral absorption has been demonstrated.^{3,4}

ESTRACE is rapidly absorbed, active at the cellular level, and follows the normal metabolic pathways in its utilization by the body. ESTRACE provides objective⁴ and clinical evidence³ of ready availability and biologic activity because estradiol can be assayed in plasma.

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ESTRACE is easy to titrate up or down as necessary for the individual patient to arrive at the lowest effective dose as soon as possible. Available in 1-mg. and 2-mg. *scored* tablets, ESTRACE is usually effective in a single dose of 2 mg. per day, administered on a cyclic basis.

References: 1. Murad F, Gilman AG: Estrogens and progestins, in Goodman L, Gilman A (eds): *The Pharmacological Basis of Therapeutics*, ed 5. New York, Macmillan Publishing Co, 1975, p 1423.

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3. Callantine MR, Martin PL, Bolding OT, et al: Micronized 17 β -estradiol for oral estrogen therapy in menopausal women. *Obstet Gynecol* 46:37, July 1975.

4. Yen SSC, Martin PL, Burnier AM, et al: Circulating estradiol, estrone and gonadotropin levels following the administration of orally active 17 β -estradiol in postmenopausal women. *J Clin Endocrinol Metab* 40:518, March 1975.

See following page for prescribing information.

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ESTRACE® (ESTRADIOL)

Estradiol...the only estrogen necessary in estrogen replacement therapy

1-mg. and 2-mg. scored tablets

Warning

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA. Three independent case control studies have shown an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for prolonged periods.^{1,3} This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade.⁴ The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose.³ In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration;³ it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equivalent doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY. The use of female sex hormones, both estrogens and progestagens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed *in utero* to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare.^{5,6} This risk has been estimated as not greater than 4 per 1000 exposures.⁷ Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis.^{8,12} Epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects.¹³⁻¹⁶ One case control study¹⁷ estimated a 4.7-fold increased risk of limb reduction defects in infants exposed *in utero* to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestagens are effective for these uses. If Estrace® is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus and the advisability of pregnancy continuation.

Clinical Pharmacology—17 β -Estradiol is the most potent physiologic estrogen and, in fact, is the major estrogenic hormone secreted by the human. Estradiol in Estrace® has been micronized and demonstrated to be rapidly and effectively absorbed from the gastrointestinal tract.¹⁷

Indications: Estrace® is indicated in the treatment of: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression which might occur during menopause, and they should not be used to treat these conditions.) 2. Atrophic vaginitis. 3. Kraurosis vulvae. 4. Female hypogonadism. 5. Female castration. 6. Primary ovarian failure. ESTRACE® HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

Contraindications: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients with progressing inoperable or radiation resistant disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

Warnings: There is now evidence that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast. However, women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms should be administered an estrogen with caution and a careful breast examination should be performed. A recent study has reported a 2 to 3-fold increase in the risk of surgically confirmed gall bladder disease in women receiving postmenopausal estrogens.¹⁸ An increased risk of post-surgery thromboembolic complications has been reported in users of oral contraceptives.^{19,20} If feasible, estrogen should be discontinued at least 4 weeks before, and not resumed until at least 4 weeks after, surgery of the type associated with an increased risk of thromboembolism. Estrogens should not be used in persons with thromboembolic disorders and they should not be used (except in treatment of malignancy) in persons with a history of such disorders in association with estrogen use or in patients with cerebral vascular or coronary artery disease. Benign hepatic adenoma should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepato-cellular carcinoma has also been reported in women taking

estrogen-containing oral contraceptives.²¹ The relationship of this malignancy to these drugs is not known at this time. There is now evidence that elevated blood pressure occurs with use of estrogens in the menopause²² and blood pressure should be monitored with estrogen use, especially if high doses are used. Diabetic patients taking estrogens should be carefully observed for decrease in glucose tolerance. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

Precautions: A complete pretreatment and periodic physical examination should be given to estrogen users with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolaou smear. Conditions which might be influenced by fluid retention such as epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop undesirable manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Patients with a history of depression should be carefully observed. Preexisting uterine fibromyomata may increase in size while using estrogen. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be administered with caution in patients with impaired liver function. Estrogens should be used with caution in patients with metabolic bone diseases that are associated with hypercalcemia or in patients with renal insufficiency. Estrogens should be used judiciously in young patients in whom bone growth is not complete. The following endocrine and liver function tests may be affected with larger doses of estrogen: a. Increased sulfinaphthalein retention; b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin; c. Increased norepinephrine-induced platelet aggregability; c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T₄ by column, or T₄ by radioimmunoassay. Free T₃ resin uptake is decreased, reflecting the elevated TBG; free T₄ concentration is unaltered; d. Impaired glucose tolerance; e. Decreased pregnandiol excretion; f. Reduced response to metyrapone test; g. Reduced serum folate concentration; h. Increased serum triglyceride and phospholipid concentration. As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

Adverse Reactions: The following additional adverse reactions have been reported with estrogenic therapy, including oral contraceptives: Breakthrough bleeding, spotting, change in menstrual flow, Dysmenorrhea; Premenstrual-like syndrome; Amenorrhea during and after treatment; Increase in size of uterine fibromyomata; Vaginal candidiasis; Change in cervical eversion and in degree of cervical secretion; Cystitis-like syndrome; Tenderness, enlargement, secretion of the breasts; Nausea, vomiting; Abdominal cramps; bloating; Cholestatic jaundice; Chloasma or melasma which may persist when drug is discontinued; Erythema multiforme; Erythema nodosum; Hemorrhagic eruption; Loss of scalp hair; Hirsutism; Steepening of corneal curvature; Intolerance to contact lenses; Headache, migraine, dizziness; Mental depression; Chorea; Increase or decrease in weight; Reduced carbohydrate tolerance; Aggravation of porphyria; Edema; Changes in libido.

Overdosage: Serious ill effects have not been reported following the ingestion of large doses of estrogen-containing oral contraceptives by young children. Overdosage of estrogen may cause nausea, and withdrawal bleeding may occur in females.

Dosage and Administration: 1. *Given cyclically for short term use only:* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause. The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible. Administration should be cyclic (e.g., 3 weeks on and 1 week off). Attempts to discontinue or taper medication should be made at 3 to 6 month intervals. The usual initial dosage range is 1 or 2 mg. daily of micronized estradiol adjusted as necessary to control presenting symptoms. The minimal effective dose for maintenance therapy should be determined by titration.

2. *Given cyclically:* Female hypogonadism; female castration; primary ovarian failure. Treatment is usually initiated with a dose of 1 or 2 mg daily of micronized estradiol, adjusted as necessary to control presenting symptoms; the minimal effective dose for maintenance therapy should be determined by titration. Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

References: (1) Ziel HK, Finkel WD: *N Engl J Med* 293:1167, 1975; (2) Smith DC, et al: *N Engl J Med* 293:1164, 1975; (3) Mack TM, et al: *N Engl J Med* 294:1262, 1976; (4) Weiss NS, et al: *N Engl J Med* 294:1259, 1976; (5) Herbst AL, et al: *N Engl J Med* 284:878, 1971; (6) Greenwald P, et al: *N Engl J Med* 285:390, 1971; (7) Lanier A, et al: *Mayo Clin Proc* 48:793, 1973; (8) Herbst A, et al: *Obstet Gynecol* 40:287, 1972; (9) Herbst A, et al: *Am J Obstet Gynecol* 117:607, 1974; (10) Herbst A, et al: *N Engl J Med* 292:334, 1975; (11) Staff A, et al: *Obstet Gynecol* 43:118, 1974; (12) Sherman AI, et al: *Obstet Gynecol* 44:531, 1974; (13) Gal I, et al: *Nature* 216:83, 1967; (14) Levy EP, et al: *Lancet* 7:611, 1973; (15) Nora J, Nora A: *Clin Endocrinol* 1941, 1973; (16) Janerich DT, et al: *N Engl J Med* 291:697, 1974; (17) Yen SSC, et al: *J Clin Endocrinol Metab* 43:118, 1975; (18) Boston Collaborative Drug Surveillance Program: *N Engl J Med* 290:15, 1974; (19) Vessey MP, et al: *Br Med J* 3:123, 1970; (20) Greene GR, Sartwell PE: *Am J Public Health* 62:680, 1972; (21) Mays ET, et al: *JAMA* 235:730, 1976; (22) Pfeffer RI, Van Den Noort S: *Am J Epidemiol* 103:445, 1976.

How Supplied: Estrace 1 mg; lavender scored tablets, NDC 0087-0755-01, bottles of 100. Estrace 2 mg; turquoise scored tablets, NDC 0087-0756-01, bottles of 100.

Full prescribing information is available in the Estrace physician package insert.

Mead Johnson
LABORATORIES

Spines and stings and sea snakes

Sherman A. Minton, M.D.

Despite what *Jaws* would have you believe, most injuries by marine animals are caused by far less impressive creatures than Great White Sharks. In typical seaside communities in the U.S., a physician may be called for a child who has stepped on a stingray, a fisherman stabbed by a scorpionfish, or an underwater photographer who backed into a cluster of sea urchins (Figure 1). Even in the landlocked Midwest, aquarium hobbyists have been snapped by moray eels or impaled with the venomous spines of lionfish. An estimated 5,600 persons are treated annually in the U.S. for marine animal envenomations. This figure, though, is probably minimal, for many of the milder cases are never seen by a physician.

This article deals mostly with injuries by venomous marine animals found along the shores of the continental U.S.; however, since work or recreation takes thousands of Americans to distant shores, this article will also

mention some exotic venomous species. Marine animals that cause poisoning when eaten will not be included here. Likewise, little will be said about the purely mechanical injuries inflicted by sharks and other sea creatures.

Venoms have evolved in various animals and serve both for prey capture and for defense. In the highly competitive marine environment they are of undoubted survival value, but for

some unfortunate humans who venture into that marine environment they can cause decided problems.

Jellyfish and coral and such

Coelenterates probably cause the greatest number of marine animal envenomations. The phylum includes sessile forms, such as hydroids, corals, and sea anemones, and pelagic forms, such as jellyfish and the Portuguese man-o-war. Some of the



Figure 1—Sea urchins and a well-camouflaged scorpionfish present a double hazard on a Caribbean reef.

Photographic credits:

Illustration Department, Indiana University

Medical Center: Figure 5

Thomas Kepler: Figures 1, 4(A), 11, 16, 17

Dr. Findlay E. Russell: Figures 3, 7, 12

Table 1 — Some important venomous coelenterates

Species	Where found	Comments
<i>Physalia physalis</i> Portuguese man-o-war Bluebottle	Around the world in tropical and sub-tropical waters	Pelagic; conspicuous gas-filled float; tentacles up to 12 meters long
<i>Millepora</i> sp. Fire corals	Around the world in tropical waters	Typical reef inhabitants
<i>Stephanoscyphus racemosus</i> <i>Halecium</i> sp. <i>Lytocarpus</i> sp. Stinging hydroids	Tropical and sub-tropical waters; more common in Indo-Pacific	Characteristic of reefs but may attach to pilings, rafts, and other structures
<i>Chironex fleckeri</i> Australian sea wasp	Waters off northern Australia	Most dangerous of coelenterates
<i>Chiropsalmus</i> sp. <i>Carybdea</i> sp. Sea wasps; box jellies	Widespread in tropical and subtropical waters, especially Indo-Pacific	Cause severe stings but less dangerous than <i>Chironex</i>
<i>Cyanea capillata</i> Lion's mane or giant jellyfish	Most of Pacific; north Atlantic	Largest of jellyfish; bell diameter up to 3 meters, tentacles up to 36 meters long
<i>Chrysaora quinquecirrha</i> Sea nettle	Tropical and north temperate waters	Common off Atlantic coast of U.S.; severe stinger; tentacles to 1.2 meters long
<i>Anemonia sulcata</i> European stinging anemone	Eastern Atlantic and Mediterranean	Common shallow-water species; can inflict a severe sting
<i>Rhodactis howesi</i> Matamutu anemone	Tropical Pacific and Indian Oceans	Often eaten in Polynesia; toxic on ingestion if uncooked; also reported to cause stings

more important species in U.S. waters are listed in Table 1.

Stinging organoids or nematocysts characterize the entire phylum but in most species are too weak to penetrate human skin. Each nematocyst injects only a minute amount of toxin; however, the aggregate discharge from a large jellyfish may total a few milliliters. Coelenterate venoms are multicomponent systems with proteins and polypeptides accounting for most of their toxicity.

Most stings occur in the water when the animals are accidentally touched by swimmers. The popularity of skin and scuba diving has increased the number of stings by sessile species such as anemones and fire corals. Stings may also be inflicted by marine animals stranded on the beach or by detached tentacles adhering to fish nets or mooring lines (Figure 2). The severity of



Figure 2—A large, gas-filled float characterizes the Portuguese man-of-war or bluebottle (*Physalia*). Stranded animals still retain their ability to sting.



Figure 3—Sting from a sea wasp. Pain is soon followed by raised lesions.



4A



4B

Figure 4—(A and B) White-tipped wands of fire coral (*Millepora*) are common on tropical reefs. Size and shape may vary greatly with ecologic conditions. (C) Contact

the sting depends chiefly upon the number of nematocysts that discharge into the skin, but species differences in venoms are also important.

Pain is usually the first symptom and varies from a faint netting sensation to a very severe burning. This is usually followed by a red, elevated skin lesion that is frequently linear in jellyfish and man-o-war stings and blotchy or punctate in anemone or fire coral stings (Figure 3 and Figure 4, A, B, and C). The lesion may require 24 hours or so for full development and may persist up to a few weeks. Vesiculation and local necrosis have been reported but are rare. Systemic symptoms accompanying severe stings include muscular cramps, cough, dyspnea, and vomiting.

In U.S. waters, most severe stings are caused by the man-o-war (*Physalia*) and the jellyfish,



4C

with fire coral results in painful wheals sometimes lasting several days. Prednisolone sprays or lotions afford symptomatic relief.

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In patients with renal disease, thiazides may precipitate azotemia. Use with caution in patients with severe renal disease or impaired hepatic function.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details, see the brief summary of prescribing information.

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This fixed combination drug is not indicated for initial therapy of hypertension. Hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see **Warnings**); anuria; routine use in an otherwise healthy pregnant woman with or without edema; hypersensitivity to methyldopa or to hydrochlorothiazide or other sulfonamide-derived drugs.

Warnings: METHYLDOPA—It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within the first three weeks of therapy, sometimes with eosinophilia or abnormalities in one or more liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually within the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction of white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Follow patients carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

HYDROCHLOROTHIAZIDE—Use with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects may develop in patients with impaired renal function. Use with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. May add to or potentiate action of other antihypertensive drugs; potentiation occurs with ganglionic or peripheral adrenergic blocking drugs. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possibility of exacerbation or activation of systemic lupus erythematosus has been reported. Lithium generally should not be given with diuretics because they reduce its renal clearance and add a high risk of lithium toxicity; read circulars for lithium preparations before use of such concomitant therapy.

Use in Pregnancy: Although no obvious teratogenic effects have been reported with the use of methyldopa, the possibility of fetal injury cannot be excluded. Thiazides cross placental barrier and appear in cord blood. In women who are or may become pregnant, weigh anticipated benefits against possible risks, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: Thiazides appear in breast milk. If use of ALDORIL is deemed essential, patient should stop nursing.

Precautions: METHYLDOPA—Should be used with caution in patients with history of previous liver disease or dysfunction (see **Warnings**). May interfere with measurement of uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites. Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has recurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

HYDROCHLOROTHIAZIDE—Perform periodic determination of serum electrolytes to detect possible electrolyte imbalance. Observe all patients for clinical signs of fluid or electrolyte imbalance, namely, hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when patient is vomiting excessively or receiving parenteral fluids. Medication such as digitalis may also influence serum electrolytes. Warning signs, irrespective of cause, are dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, in severe cirrhosis, with concomitant corticosteroids or ACTH, or with inadequate oral electrolyte intake. Hypokalemia can sensitize or exaggerate response of heart to toxic effects of digitalis (e.g., increased ventricular irritability). Hypokalemia may be avoided or treated by use of potassium supplements, such as foods with a high potassium content. Any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease). Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life threatening. In actual salt depletion, appropriate replacement is the therapy of choice.

Hyperuricemia may occur or frank gout may be precipitated in certain patients. Insulin requirements in diabetic patients may be increased, decreased, or unchanged; latent diabetes mellitus may become manifest. Thiazides may increase responsiveness to tubocurarine. Antihypertensive effects of the drug may be enhanced in postsympathectomy patients. May decrease arterial responsiveness to norepinephrine; this diminution is not sufficient to preclude effectiveness of the pressor agent for therapeutic use. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. Pathological changes in the parathyroid glands with hypercalcemia and hypophosphatemia have been observed in a few patients on prolonged therapy; thiazides should be discontinued before testing for parathyroid function.

Adverse Reactions: METHYLDOPA—*Central nervous system:* Sedation, headache, asthenia or weakness; dizziness, lightheadedness, symptoms of cerebrovascular insufficiency, paresthesias, parkinsonism, Bell's palsy, decreased mental acuity, involuntary choreoathetotic movements; psychic disturbances, including nightmares and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angina pectoris. Orthostatic hypotension (decrease daily dosage). Edema (and weight gain) usually relieved by use of a diuretic. (Discontinue methyldopa if edema progresses or signs of heart failure appear.) *Gastrointestinal:* Nausea, vomiting, distention, constipation, flatulence, diarrhea, mild dryness of mouth, sore or "black" tongue, pancreatitis, sialadenitis. *Hepatic:* Abnormal liver function tests, jaundice, liver disorders. *Hematologic:* Positive Coombs test, hemolytic anemia, leukopenia, granulocytopenia, thrombocytopenia. *Allergic:* Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlargement, gynecomastia, lactation, impotence, decreased libido, dermatologic reactions including eczema and lichenoid eruptions, mild arthralgia, myalgia.

HYDROCHLOROTHIAZIDE—*Gastrointestinal system:* Anorexia, gastric irritation, nausea, vomiting, cramping, diarrhea, constipation, jaundice (intrahepatic cholestatic jaundice), pancreatitis, sialadenitis. *Central nervous system:* Dizziness, vertigo, paresthesias, headache, xanthopsia. *Hematologic:* Leukopenia, agranulocytosis, thrombocytopenia, aplastic anemia. *Cardiovascular:* Orthostatic hypotension (may be aggravated by alcohol, barbiturates, or narcotics). *Hypersensitivity:* Purpura, photosensitivity, rash, urticaria, necrotizing angitis (vasculitis) (cutaneous vasculitis), fever, respiratory distress including pneumonitis, anaphylactic reactions. *Other:* Hyperglycemia, glycosuria, hyperuricemia, muscle spasm, weakness, restlessness, transient blurred vision. Whenever adverse reactions are moderate or severe, thiazide dosage should be reduced or therapy withdrawn.

Note: Tolerance may occur, usually between the second and third month of therapy. Increasing dosage of either component separately or together frequently restores effective control. Patients with impaired renal function may respond to smaller doses. Syncope in older patients may be related to increased sensitivity and advanced arteriosclerotic vascular disease; this may be avoided by lower doses.

How Supplied: Tablets ALDORIL®-15, containing 250 mg methyldopa and 15 mg hydrochlorothiazide, bottles of 100 and 1000; Tablets ALDORIL®-25, containing 250 mg methyldopa and 25 mg hydrochlorothiazide, bottles of 100 and 1000.

For more detailed information, consult your MSD representative or see full prescribing information.

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Chrysaora quinquecirrha. Most dangerous of the jellyfish are the sea wasps, *Chironex fleckeri* and *Chiropsalmus quadrigatus*. They have caused about 50 well-authenticated fatalities in the region between the Philippines and northern Australia. A less dangerous type of sea wasp, *Carbydea marsupialis*, occurs in the Caribbean (Figure 5).

Coral cuts

Coral cuts occur among divers, fishermen, and others whose activities bring them into contact with living coral. These injuries are not particularly painful, but they heal slowly and often result in ulcers. The pathogenesis is not well understood. A foreign body reaction plus bacterial infection may be chiefly responsible, though the possibility of sensitization to antigens on the surface of live coral cannot be discounted. Envenomation from the nematocysts is probably not significant. In sport divers and tourists, the ulcers usually remain shallow and heal promptly, especially if the victim returns to a temperate climate. In residents of tropical seacoasts, however, large, deep, indolent ulcers are not uncommon. This may result from repeated trauma and infection with underlying malnutrition.

Lesions from yaws, cutaneous larva migrans, and other conditions are sometimes attributed to coral injuries or "coral worms." In the tropics, folk tales are often told of coral growing in wounds or body orifices. These may cause the uninformed person much anxiety.

Clinging tentacles

In most severe coelenterate stings, tentacles remain attached to the skin. The undischarged nematocysts in these tentacles



Figure 5—This sea wasp, probably *Carbydea marsupialis*, inflicted a severe sting on a diver at Montego Bay, Jamaica. Jellyfish of this type have unusually heavy tentacles with many nematocysts.

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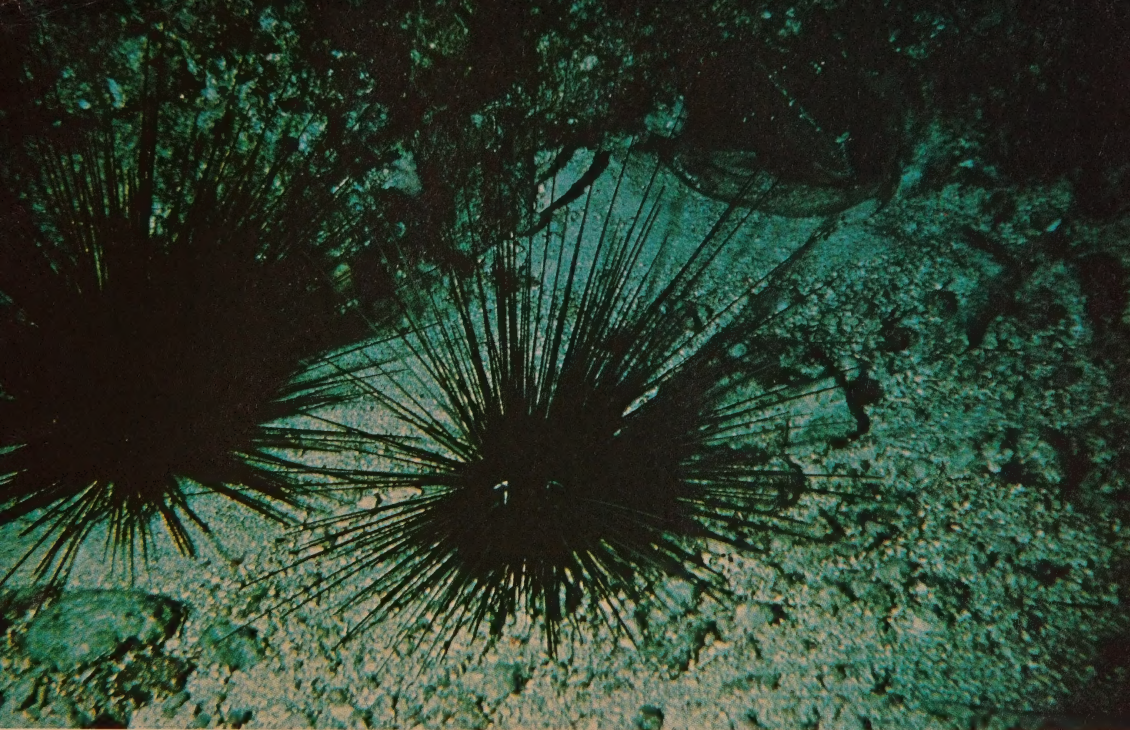


Figure 6—Long-spined sea urchins such as *Diadema* are a common cause of injuries. Envenomation is minimal, but spines often break off in the tissues.

must be inactivated promptly. This can be best accomplished by immediately applying alcohol. On the research vessel *Alpha Helix* during diving operations in Australian and Philippine waters, a 1-liter plastic bottle of methyl alcohol was kept in all dive boats. Salt, sugar, or dry sand may be substituted for alcohol but are less effective. After about 15 minutes, the inactivated tentacles may be scraped off.

Combat dyspnea by maintaining an open airway, administering oxygen, and starting mouth-to-mouth resuscitation if necessary. Rapidly acting antihistaminics such as promethazine or diphenhydramine given parenterally appear to be the best pharmacologic antidotes. Hydrocortisone and its analogues, epinephrine, and intravenous calcium gluconate have been re-

ported to be effective. An antitoxin against *Chironex fleckeri* venom has been produced in Australia (Commonwealth Serum Laboratories, Parkville, Victoria). It neutralizes the venom of *Chiropsalmus* but not *Chrysaora* and Portuguese man-o-war venoms.

Many local applications have been used for milder coelenterate stings. In the U.S., prednisolone or antihistaminic sprays, lotions, or creams are favored. In Australia, an alcoholic solution of benzocaine or a mixture of picric acid, camphor, and denatured alcohol is widely used. Meat tenderizer dissolved in water is used by some U.S. swimmers, divers, and surfers. All these preparations give some degree of relief but they must usually be repeated every 2 to 3 hours. Coral cuts usually respond well to cleansing and ap-

plication of neomycin-bacitracin-polymyxin ointment.

Virtually any type of protective clothing will ward off coelenterate stings. Wet suits, body stockings, and various combinations of jeans and jerseys all have their advocates. Certain inadequately understood combinations of wind, currents, tide, and light favor the inshore aggregation of some dangerous coelenterates so that bathers may be stung in shallow water or even as they walk on the shore.

Sea urchins

Another common type of marine animal injury is that inflicted by sea urchin spines. These animals are often very plentiful in shallow water and tend to be more active at night. The long-spined genera, such as *Echinothrix* and *Diadema*, are usually involved in human injuries (Figure 6). Spe-

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When aspirin is no longer appropriate in the long-term management of rheumatoid arthritis, Naprosyn* (naproxen) represents a logical therapeutic choice for these sensible reasons:

Confirmed clinical efficacy

Naprosyn has been shown to be comparable to aspirin in reducing the duration of morning stiffness and pain associated with inflammation.

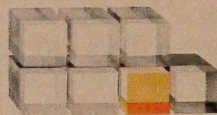
Introduced internationally 5 years ago — currently in use in more than 40 countries around the world. Documented in over one hundred clinical papers. Reviewed in-depth at many international and domestic symposia.

Since its introduction, nearly one-million prescriptions written in the United States.

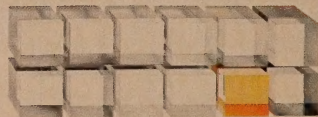
Well tolerated by most patients

In 737 clinical trial patients treated:

GI
side effects
1 patient in 7



CNS
side effects
1 patient in 12



Less frequent and less severe adverse reactions than aspirin

The frequency and severity of the *milder* gastrointestinal adverse effects (nausea, dyspepsia, heartburn) and nervous system adverse effects (tinnitus, dizziness, lightheadedness) were less than in the aspirin-treated patients. It is not known whether Naprosyn causes less peptic ulceration than aspirin. (See warnings, adverse reactions, and precautions sections in Prescribing Information following next page).

Naprosyn[®] B.I.D.

(naproxen)

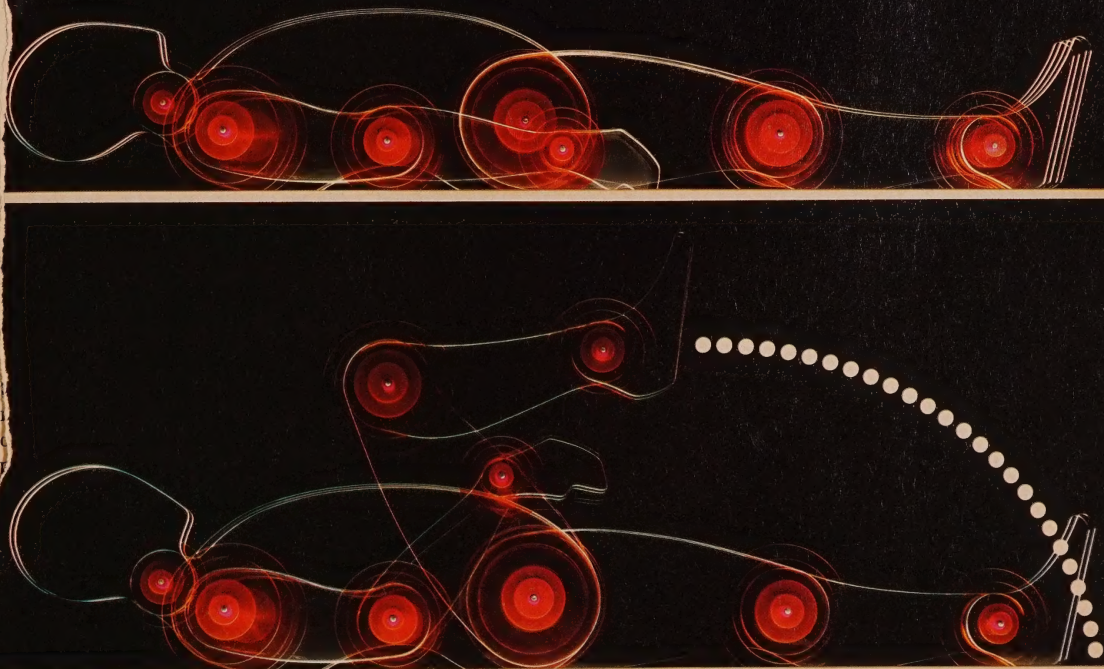
*Safety and efficacy of Naprosyn have not been established in patients designated by the American Rheumatism Association as Functional Class IV.

**Unique B.I.D.
regimen to enhance
patient compliance**

13-hour half-life provides sustained 24-hour blood levels.

See following page for summary of prescribing information.

Illustration emphasizes the importance exercise often plays in a well integrated arthritis-care program.



After aspirin...

250 mg. tablets

Naprosyn® B.I.D.

(naproxen)

Indications and Usage

Naprosyn (naproxen) is indicated for relief of the signs and symptoms of rheumatoid arthritis. It is indicated in the treatment of acute flares and in the long-term management of the disease. The safety and effectiveness of Naprosyn have not been established in those rheumatoid arthritis patients which are designated by the American Rheumatism Association as Functional Class IV (incapacitated, largely or wholly bedridden or confined to a wheelchair; little or no self care). Controlled trials to establish the safety and effectiveness of Naprosyn in children have not been conducted.

Contraindications

Naprosyn is contraindicated in patients who have shown hypersensitivity to it. Because the potential exists for cross-sensitivity reactions, Naprosyn should not be given to patients in whom aspirin or other non-steroidal anti-inflammatory drugs induce the syndrome of asthma, rhinitis or urticaria.

Warnings

Naprosyn should be given under close supervision to patients prone to upper gastrointestinal tract disease and only after consulting the "Adverse Reactions" Section. Gastrointestinal bleeding, sometimes severe, and occasionally fatal, has been reported in patients receiving Naprosyn (see Adverse Reactions). In patients with active peptic ulcer and active rheumatoid arthritis, attempts should be made to treat the arthritis with non-ulcerogenic drugs, such as gold. If Naprosyn must be given, the patient should be under close supervision for signs of ulcer perforation or severe gastrointestinal bleeding.

Precautions

The safety of this drug in pregnancy and lactation has not been established and its use during these events is therefore not recommended. Reproduction studies have been performed in rats, rabbits and mice. In rats, pregnancy was prolonged when naproxen was given before the onset of labor; when it was given after the delivery process had begun, labor was protracted. Similar results have been found with those non-steroidal anti-inflammatory drugs which inhibit prostaglandin synthetase.

Naproxen readily crosses the placental barrier. It has been found in the milk of lactating women at a concentration of approximately 1% of that found in the plasma.

In vitro studies have shown that Naprosyn, because of its affinity for protein, may displace from their binding sites other drugs which are also albumin-bound and may consequently lead to drug interactions. Theoretically, Naprosyn itself could likewise be displaced. In a patient receiving bishydroxycoumarin or warfarin, the addition of Naprosyn to therapy could prolong the prothrombin time. Patients receiving both drugs should be under careful observation. Similarly, patients receiving Naprosyn and a hydatoint, sulfonamide or sulfonylurea should be observed for signs of toxicity to these drugs.

In chronic studies in mice and rats, high doses of Naprosyn caused nephritis. Since Naprosyn is eliminated to a large extent from the body by urinary excretion via glomerular filtration, the drug should be used with great caution in patients with significantly impaired renal function and the monitoring of serum creatinine and/or creatinine clearance is advised in these patients. Additionally, a reduction in daily dosage should be anticipated

to avoid the possibility of excessive drug accumulation. In clinical trials a few patients developed mild elevations in BUN. The significance of this is unknown.

If steroid dosage is reduced or eliminated during Naprosyn (naproxen) therapy, the steroid dosage should be reduced slowly and the patients must be observed closely for any evidence of adverse effects, including adrenal insufficiency and exacerbation of symptoms of rheumatoid arthritis.

Studies to date have not shown changes in the eye attributable to Naprosyn administration; however, because of adverse eye findings in animal studies with some other non-steroidal anti-inflammatory drugs, it is recommended that ophthalmologic studies be carried out within a reasonable period of time after starting chronic Naprosyn therapy and at periodic intervals thereafter.

Caution should be exercised by patients whose activities require alertness if they experience drowsiness, dizziness, vertigo or depression during Naprosyn therapy.

Peripheral edema has been observed in some patients receiving Naprosyn. Although sodium retention has not been found in metabolic studies, it is possible that patients with questionable or compromised cardiac function may be at a greater risk when taking Naprosyn.

Naprosyn decreases platelet aggregation and prolongs bleeding time. This effect should be kept in mind when bleeding times are determined.

Patients with initial hemoglobin values of 10 grams or less who are to receive long-term Naprosyn therapy should have hemoglobin values determined frequently.

The administration of Naprosyn may result in increased urinary values for 17-ketogenic steroids because of an interaction between the drug and/or its metabolites with m-dinitrobenzene used in this assay. Although 17-hydroxycorticosteroid measurements (Porter-Silber test) do not appear to be artifactually altered, it is suggested that Naprosyn therapy be temporarily discontinued 72 hours before adrenal function tests are performed.

Adverse Reactions

Adverse reactions related to the gastrointestinal tract were reported in approximately 1 in 7 patients. In decreasing order of frequency they were: heartburn, nausea, dyspepsia, abdominal pain, constipation, stomatitis, diarrhea, vomiting, melena, gastrointestinal bleeding.

Among 737 patients treated with Naprosyn during the course of clinical trials in the United States (256 treated for more than two years), 15 cases of peptic ulceration were reported. About half were on concomitant corticosteroid and/or salicylate therapy and about a third had a prior history of peptic ulcer. Gastrointestinal bleeding, including seven potentially serious cases, was also reported in this population. These were not always preceded by premonitory gastrointestinal symptoms. Although most of the patients with serious bleeding were receiving concomitant therapy and had a history of peptic ulcer disease, it should be kept in mind that Naprosyn also has the potential for causing gastrointestinal bleeding on its own. In foreign marketing experience, there have been a number of fatalities due to gastrointestinal bleeding in patients who were receiving Naprosyn. A cause-effect relationship in these patients was not established.

Adverse reactions related to the central nervous system were reported in approximately 1 in 12 patients. In decreasing order of frequency they were: headache, drowsiness, dizziness, lightheadedness, vertigo, inability to concentrate, depression.

Adverse reactions related to the skin were reported in approximately 1 in 20 patients. In decreasing order of frequency they were: itching (pruritus), skin eruptions, sweating, ecchymoses, skin rashes, urticaria, purpura.

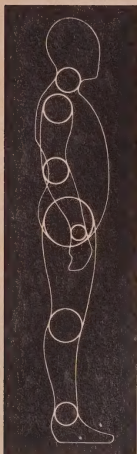
Adverse reactions related to special senses were reported in approximately 1 in 20 patients. In decreasing order of frequency they were: tinnitus, visual disturbances, hearing disturbances.

Adverse reactions related to the cardiovascular system were reported in approximately 1 in 50 patients. In decreasing order of frequency they were: edema, palpitations, dyspnea.

Thirst was reported in approximately 1 in 100 patients.

Rare reactions include angioneurotic edema, thrombocytopenia, agranulocytosis and jaundice.

SYNTEX
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HUMACAO, P.R. 00661



cies with short or blunt spines, however, may have venom associated with the pedicellariae or tube-feet on the ventral surface. Species of the genus *Tripaneustes* have been reported to cause fatal envenomation. The venom of sea urchin spines appears to be of very low toxicity for man; the pedicellarial venoms are reported to be highly toxic proteins or polypeptides.

The pain of a sea urchin spine injury is usually not greatly out of proportion to the mechanical injury. The puncture wound is dark and often surrounded by a purplish ring that fades in a short time. Spines frequently break off in the tissues and are difficult to extract because they are extremely brittle and ringed with minute spinules. Small fragments are probably removed by phagocytosis and rarely cause trouble; larger fragments may incite a granulomatous reaction. Pedicellarial envenomation is rare and usually occurs when urchins are gathered with the bare hands for food or other purposes (Figure 7). Reported symptoms include pain, giddiness, cranial nerve palsies, and respiratory difficulty.

Minor spine wounds should be treated conservatively. In cases where large pieces of spines have become imbedded in the tissues, the fragments should be removed surgically. There is no specific treatment for pedicellarial envenomation.

Cone shells

Certain of the cone shells are rare and are highly prized by collectors. Handsome as they are, a few of the cone shells are dangerous. Most cones have hollow, venom-charged darts, up to 11 mm long in some species, that can be discharged into potential prey or enemies. The venom is a protein

with paralytic activity. Only the larger species, which prey on fish, are believed dangerous, and only a single species, *Conus geographus*,

has unquestionably caused injuries fatal to man (Figure 8). This species has an extensive distribution in the tropical

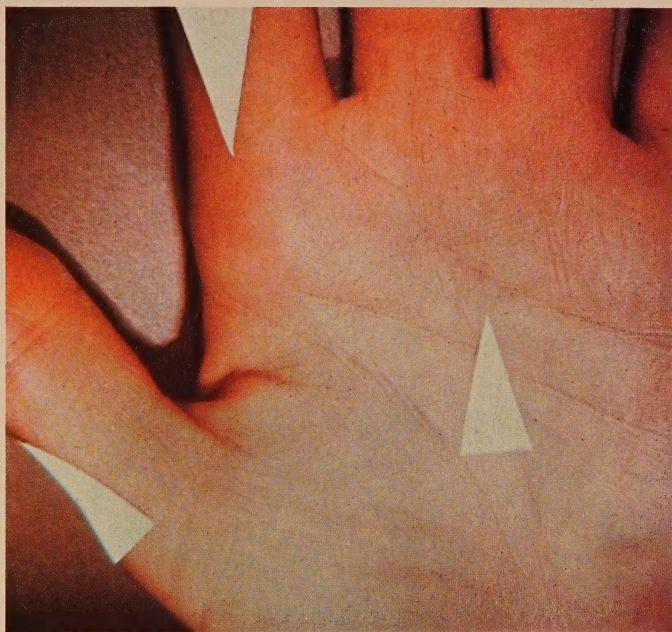


Figure 7—Pedicellarial envenomation is rare and usually occurs when urchins are gathered with the bare hands.



Figure 8—Although many species of cone shells can inflict venomous stings, only this species, *Conus geographus*, has unquestionably caused human fatalities.



Figure 9—In most stingrays, the venomous spine is attached to the middle third of the tail. In some species, multiple spines occur.

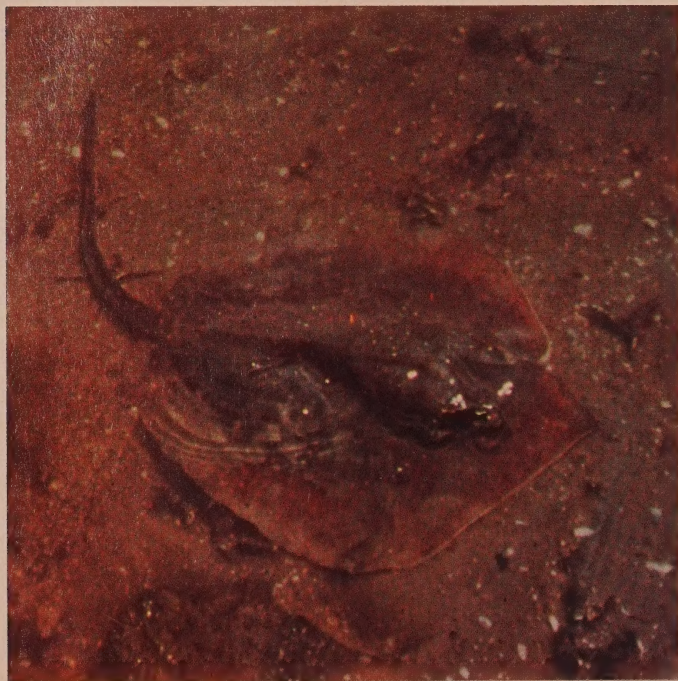


Figure 10—Lying on the bottom of a shallow coastal stream, this stingray could easily be stepped on, especially if the water was turbid.

Indo-Pacific but does not reach the continental U.S. A few species in U.S. coastal waters are reported to cause wasp-like stings.

Cone shell stings occur when the animals are picked up and handled. Local symptoms, pain and swelling, are variable and not proportional to the degree of systemic involvement. Cranial nerve palsy, muscular weakness, and respiratory distress occur in severe cases. Treatment is symptomatic; support of respiration is important in serious poisoning. Systemic venom effects wear off in a few hours.

Octopuses and sponges

Some species of octopus can inflict venomous bites, and the blue-ringed octopus (*Hapalochlaena*), a small Australian species, has caused fatalities. Although the venoms are chemically different, the symptoms are similar to those of cone-shell poisoning. Treatment is symptomatic.

Contact with several species of sponges may cause painful dermatitis. Symptoms are more delayed in onset and prolonged than those caused by contact with fire coral or other sessile coelenterates. The chemistry of sponge toxins is not well known. Treatment of the dermatitis is symptomatic; corticoids locally and by mouth are reported to be effective.

Annelids

A few marine annelids, such as the bloodworm, *Glycera dibranchiata*, which is used for bait in parts of Canada and the U.S., can inflict venomous bites accompanied by swelling and pain. Other marine annelids, which are for the most part tropical in distribution, have bristles that are capable of causing a painful

dermatitis on contact. There is no specific treatment for annelid injuries; however, serious envenomation has not been reported.

Stingrays and other fishes

Stingrays are a group of primitive fishes related to sharks. They are widely distributed, and several species are common in U.S. coastal waters. The sting, a serrate, bony spine, is usually attached to the dorsal surface of the middle third of the ray's tail (Figure 9). Spines of large rays may be 30 cm or more long. Spongy, venom-producing tissue covers the spine and is concentrated in the ventrolateral grooves. In stinging, the tail is whipped forward and downward, driving the spine into the tissues. As it is withdrawn, the serrations produce a lacerated wound within which some of the venom-laden tissue is deposited. In human injuries, it is most unusual for the spine to be left in the wound. A large ray can deliver a blow powerful enough to penetrate the thoracic or abdominal wall.

Pure preparations of stingray venom are unstable and difficult to obtain. The principal toxins appear to be proteins, and low molecular weight substances such as serotonin have also been detected.

Human injuries usually occur when the ray, buried in sand or mud, is stepped on (Figure 10). Stings may also be inflicted by rays speared or caught in nets or on lines. There is no reliable report of a ray stinging while swimming free (Figure 11). The wound may be a puncture or a laceration several centimeters long (Figure 12). It may bleed freely at first but soon becomes surrounded by a bluish-white area of ischemia. Pain is severe

and tends to increase during the next 90 minutes or so. It may be accompanied by nausea and faintness. Moderate edema of the injured foot may occur. Systemic absorption of venom may cause vomiting, salivation, diarrhea, muscle cramps and fasciculations, dyspnea, and loss of consciousness. The wound often ulcerates and heals slowly. Fatalities are nearly always associated with penetration of the abdominal or

thoracic cavity or with tetanus or other infections. Toxemia may not occur even with considerable mechanical damage, presumably because rays sometimes lose all or most of the venom-containing tissue from their stings.

First aid for stingray injuries is prompt and thorough irrigation of the wound with sea water or any comparable liquid. If mucoid grayish pieces of the sting-sheath are seen, they should be

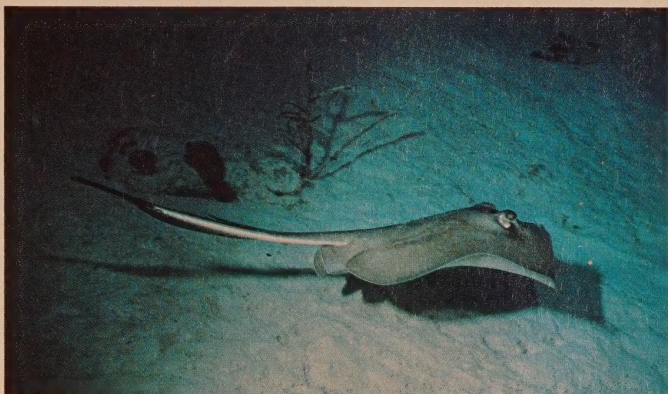


Figure 11—Swimming gracefully over powdery sand, this stingray (probably *Dasyatis sayi*) will not use its venomous spine unless pinned against the bottom.



Figure 12—The wound from a stingray may bleed freely. Pain is severe and increases for a time.

Table 2 — Some venomous fishes

Species	Where found	Comments
<i>Galichthys felis</i> Sea catfish	Cape Cod to Gulf of Mexico and Panama	Serrate, venomous dorsal and pectoral spines
<i>Plotosus lineatus</i> Striped marine catfish (Figure 13)	Indo-Pacific; often seen in schools about reefs	Strongly serrate spines; highly toxic venom
<i>Trachinus draco</i> Greater weeverfish	North Sea to Mediterranean; usually in deep water	Venomous dorsal and opercular spines; commercially important food fish
<i>Pterois volitans</i> <i>P. antennata</i> Lionfish, zebrafish, turkeyfish (Figure 14)	Tropical and subtropical Indo-Pacific; often seen about reefs	Distinctive and brightly colored; popular in aquarium trade; long, slender, venomous dorsal spines; occasionally aggressive
<i>Scorpaena guttata</i> California scorpionfish	Much of California coast	Venomous dorsal spines; common, often taken by fishermen; may be attracted to light
<i>Scorpaena brasiliensis</i> Caribbean scorpionfish	Virginia to Brazil; West Indies	Bottom-dwelling; may spread pectoral fins in threat gesture
<i>Scorpaenopsis cirrhosa</i> Hawaiian scorpionfish False stonefish (Figures 15 and 16)	Tropical and subtropical Indo-Pacific	Reef species; highly variable in color
<i>Synanceja horrida</i> <i>S. verrucosa</i> Stonefish	Tropical Indo-Pacific; often in shallow, rather turbid water, partially buried	Large venom glands at base of stout dorsal spines; most dangerous of venomous fishes
<i>Thalassophryne maculosa</i> Caribbean toadfish	Caribbean Sea; bottom- dwelling in turbid water	Hollow, venomous dorsal spines; comparatively weak venom

wiped or pulled away. Intermittent immersion of the injured area in water as hot as can be tolerated is often more effective in relieving pain than any medication. Infiltration with local anesthetic or nerve block also gives relief. There are no specific antagonists to stingray venom. Rest and elevation of the injured part, analgesia, and countermeasures against infection are important. Debridement and closure of the wound with interrupted sutures are often necessary. Surgical exploration is mandatory if the sting has penetrated the chest or abdomen.

In addition to stingrays, more than 100 other species of fishes have venomous spines variously situated on their bodies but usually associated with the fins.

These species are cosmopolitan in distribution; some of the more important ones are listed in Table 2. Nearly all are bottom-frequenting fishes that conceal themselves in sand, mud, or vegetation, or lurk in coral crevices. Human injuries occur when the fish are taken on lines or in nets, or when swimmers, waders, or divers disturb the fish. None of these fish make unprovoked attacks, but some will behave aggressively if they are annoyed. A few showy species such as the lionfish (*Pterois* sp.) are popular among aquarium hobbyists who may be injured by their pets. Others are used for food, and persons buying fresh fish in markets have been injured.

As with stingrays, the venom-secreting tissue surrounds a

grooved or hollow spine. The venoms are highly labile proteins.

Intense, throbbing, radiating pain is the outstanding symptom of fish stings. Ichthyologists who have sustained such injuries write of "an insane desire to ease the mounting agony by rolling on the ground" or "this was much worse than anything previous . . . just short of driving oneself completely mad." The pain may persist for several hours and is accompanied by edema, sometimes followed by vesication and local necrosis. Systemic manifestations with severe stings include vomiting, headache, sweating, dyspnea, cyanosis, hypotension, and collapse. Despite the severity of symptoms, there are few well-documented fatalities.

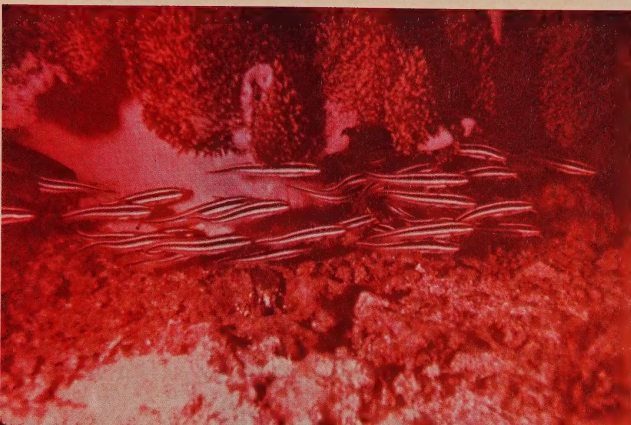


Figure 13—The striped marine catfish (*Plotosus lineatus*) characteristically aggregate in dense schools. Their venomous dorsal and pectoral spines can inflict painful injuries.



Figure 14—The lionfish or turkeyfish are the most spectacular of venomous fishes with their long fins and brilliant colors. The injuries they inflict are extremely painful; however, fatalities have not been reported. The species shown here is *Pterois antennata*.

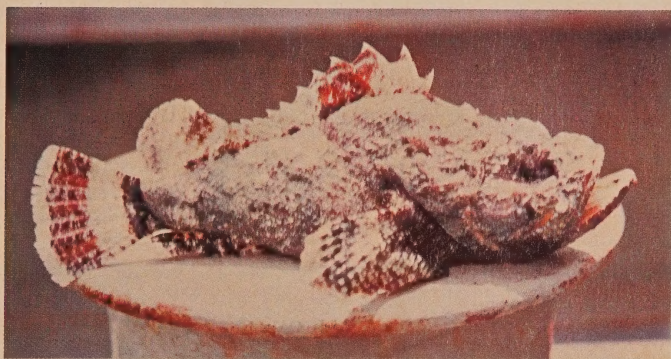


Figure 15—This Australian scorpionfish (*Scorpaenopsis* sp.) shows the venomous dorsal spines and general configuration of the group.



Figure 16—Blending closely with its background, a scorpionfish (probably *Scorpaena plumieri*) hopes to avoid notice. However, it may behave aggressively if sufficiently threatened.



Figure 17—A moray eel peers from a clump of coral. Although not venomous, these large eels can inflict a severe bite.



Figure 18—Hardwicke's sea snake (*Lapemis hardwicki*) is a highly dangerous species common in coastal waters from Vietnam to northern Australia. The broad, flat tail characterizes snakes of this family.



Figure 19—The yellow-bellied or pelagic sea snake (*Pelamis platurus*) is the only species found in American waters. It is a small sea snake and not considered particularly dangerous.

nearly all of these have been ascribed to the stonefish *Synanceja*. (In the Caribbean region, fishermen and divers often give the name "stonefish" to various venomous scorpionfish and toadfish. The dangerous genus *Synanceja* is native to the tropical Indo-Pacific and does not reach the continental U.S. or Hawaii.)

The pain of fish-sting injuries is best relieved by intermittent application of hot water to the limit of the patient's tolerance; ordinary analgesics and anesthetics are said to provide little relief. A stonefish antivenin is produced by Commonwealth Serum Laboratories of Australia. It is given in a 2- to 4-ml intravenous dose. Its effectiveness against other venomous fish is unproved, however. Infiltration with emetine hydrochloride solution (65 mg/ml) of the area around wounds from venomous fish has been recommended. Take general supportive measures, give symptomatic treatment, and take measures to prevent infection.

Most protective clothing worn by swimmers and divers affords only partial protection against stingray and other fish envenomations. These persons, as well as fishermen and aquarium keepers, should be educated regarding the hazard involved.

Eels and sea snakes

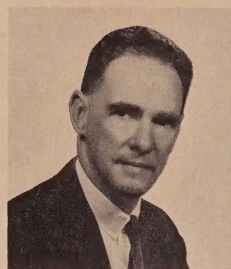
Morays, large eels up to 2 meters (or more than 6 feet) in length, are often encountered about coral reefs (Figure 17). They have powerful jaws and sharp teeth. They are not aggressive but have been known to bite hands or feet thrust into the holes and crevices they inhabit. Since Classical times these eels have been considered venomous; however, anatomic, toxicologic, and clinical

investigations have not confirmed this. Moray eels should be treated with caution. The bite of a large eel can cause considerable mechanical damage with potential for secondary infection. Debridement, suturing, and antimicrobial measures may be needed.

Sea snakes probably take a greater toll of human life than any other type of venomous marine animal. This family of about 50 species is entirely Indo-Pacific in distribution, with the greatest concentration of species in the coastal waters of southern Asia and northern Australia (Figure 18). One widely distributed species occurs in numbers along the Pacific coast of Mexico and Central America with stragglers sometimes showing up in Hawaii and extreme southern California (Figure 19). Some sea snakes are small and have a poorly developed venom apparatus; others will bite only under extreme provocation; a few are quite dangerous. Evidence indicates that about a half dozen species account for nearly all human fatalities. Most times fishermen who have taken the reptiles in their nets or traps are bitten; occasionally bathers and divers are attacked.

The venom apparatus of sea snakes is essentially that of cobras and other elapid snakes—namely, short, relatively immobile fangs in the anterior part of the upper jaw and temporal venom glands. Polypeptide neurotoxins similar to those of elapids are present in sea snake venoms, but manifestations of sea snake poisoning in man indicate other toxins may be involved as well.

Sea snake bites cause little local pain or edema. After a latent period of 15 minutes to several hours, patients complain of



Dr. Minton is professor in the department of microbiology at the Indiana University School of Medicine. He is also research associate in the department of herpetology of the American Museum of Natural History. He served as consultant to the U.S. Navy for their official publication on poisonous snakes of the world.

muscular soreness and weakness, with pain on passive movement of the limbs. Signs of systemic poisoning are ptosis, trismus, diminished tendon reflexes, and myoglobinuria. Renal damage and hyperkalemia secondary to muscle necrosis characterize the more severe cases. In patients with systemic envenomation, the case fatality rate is 15% to 20%. Many persons bitten, however, have few or no symptoms because sea snakes often inject little or no venom when they bite.

The first aid measures commonly advocated for snakebite in the U.S. are of no value in sea snake bites, because the venom is so rapidly absorbed. An antivenin that neutralizes the venom of most medically important sea snakes is produced by Commonwealth Serum Laboratories of Australia. Antivenins against venoms of land snakes, except the tiger snake and a few other Australian species, are ineffective against sea snake venoms. Hemodialysis and other supportive measures are beneficial in sea snake bites with systemic involvement.

Anal fissure

Anal fissure is a common complaint in men and women, young and old. It may be acute or chronic, and it usually results from anorectal inflammatory disease.

Acute fissure of the anal epithelium may simply be the result of a tear from the passage of an unusually large stool—with no anorectal pathology. Medical treatment consists of adjusting the patient's diet, if necessary, and prescribing lubricants and stool softening agents, all of which give the injured epithelium a chance to heal.

Chronic fissures, on the other hand, are usually secondary to an inflammation of the anal crypts. These fissures expose sensory nerve endings, resulting in an abnormal reflex response of rectal sphincter mechanism (demonstrated by rectosphincteric manometric studies). These persistent internal anal sphincter spasms cause normal stools to tear the epithelium. Cryptitis results in fibrosis of the distal margin and narrowing or stricture of the anal canal. Surgical treatment is usually necessary when chronic or recurrent anal fissures originate with cryptitis, and it may include lateral subcutaneous internal anal sphincterotomy or anoplasty.

—James M. Hampton, M.D.
Baylor College
of Medicine



2-minute test

How do you score on this quick quiz on diagnosis and treatment? Answers on page 136.

1. A first attack of gouty arthritis usually
 - ☐ Develops suddenly, reaches a peak within 10 minutes, and then subsides
 - ☐ Develops gradually over several days
 - ☐ Develops rapidly, peaking from 30 minutes to several hours after onset
 - ☐ Affects several joints
2. Patients with gout should avoid
 - ☐ Thiazide diuretics
 - ☐ Whiskey
 - ☐ Wine
 - ☐ Starchy foods
3. Which of the following drugs is best for treatment of a first attack of gout—because it will both relieve symptoms and confirm the diagnosis?
 - ☐ Phenylbutazone
 - ☐ Corticotropin
 - ☐ Colchicine
 - ☐ Aspirin
4. Compared to ampicillin, amoxicillin
 - ☐ Causes less side effects
 - ☐ Costs less
 - ☐ Is absorbed better
 - ☐ Has a wider antibacterial spectrum
5. Urinary tract infection with *Klebsiella* would be a clear indication for
 - ☐ Cephalexin or cephadrine
 - ☐ Ampicillin
 - ☐ Doxycycline
 - ☐ Tobramycin
6. Confirmatory evidence for a diagnosis of cardiac asthma would include
 - ☐ Severe hypotension
 - ☐ Murmurs indicating severe valvular heart disease
 - ☐ ECG evidence of a past myocardial infarction
 - ☐ A history of allergies
7. Drugs useful in treating a cardiac asthma attack include
 - ☐ Morphine
 - ☐ Diuretics
 - ☐ Aminophylline
 - ☐ Nitroglycerin

Flu vaccine for zoster?

Sir:

Is influenza vaccine of any value in treating herpes zoster?

—H.J. Stein, M.D.
St. Louis

The value of influenza vaccine for treating herpes zoster is debatable. Nonspecific immunologic responses have been evoked by such measures as intravenous typhoid vaccine and intramuscular injections of sterile milk. No carefully controlled

studies were done of these methods, and they were ultimately discarded.

Influenza virus is prepared from the allantoic fluid of the chick embryo infected with influenza viruses. The viruses are inactivated with formaldehyde and concentrated.

This preparation, containing a good bit of foreign protein, again invokes a nonspecific response when injected.

The only time I saw it so used,

1 ml was given daily for 3 or 4 days, until a temperature of 101° F was reached on any one day. Headache, malaise, and chills accompanied the reaction in this case.

Since there is some risk of anaphylaxis with this approach, and since there is no clearly documented evidence of its effectiveness, I would not recommend it.

—Robert Raskind, M.D.
Bakersfield, Calif.



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Growing pains or psychologic problem?

Ivan Fras, M.D.

"What should we do about Johnny? He's so aggressive!" "I worry about Mary's excessive shyness." "Bobby is 3 years old and he hasn't started to talk yet. We're wondering if he needs special training?"

You have probably heard all these or very similar complaints from parents. Should you advise them that their child will outgrow certain problems? Or

would such advice be misleading, if not outright detrimental?

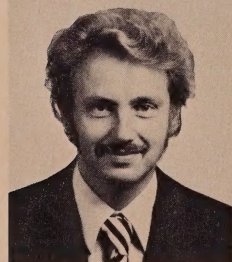
Before you can answer their questions, you must, of course, consider constitutional variations in temperament, the rate of development or actual developmental lag without behavioral disorder, and the hyperactivity syndrome.

People differ

Constitutional variations are just what the name implies. Much as the size, weight, intellectual endowment, and hair and eye color vary, so do a child's speed and pattern of response to stimuli. Some children respond quickly and "nervously" to almost everything; others tend to be "slow" and "phlegmatic."

Let me give you some examples.

- **Case 1.** A 7-year-old boy was brought to me because he was very sensitive, easily hurt (especially by peers), and often had difficulties getting along with his peers. His teachers were concerned about his "immaturity." He was frequently described as daydreaming and not getting his work done on time. He was,



Dr. Fras is clinical assistant professor of psychiatry at Upstate Medical Center, Syracuse, New York, and chief of the psychiatric services for children at the Broome County Mental Health Clinic, Binghamton. He has been certified in psychiatry and child psychiatry by the American Board of Psychiatry and Neurology.

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Peritrate® (pentaerythritol tetranitrate)	10 mg

CAUTION: Federal law prohibits dispensing without prescription.
Description: Each tablet of Peritrate SA-Sustained Action contains pentaerythritol tetranitrate 80 mg (20 mg in immediate release layer and 60 mg in sustained release base). Each tablet of Peritrate 40 mg contains pentaerythritol tetranitrate 40 mg. Each tablet of Peritrate 20 mg contains pentaerythritol tetranitrate 20 mg. Each tablet of Peritrate 10 mg contains pentaerythritol tetranitrate 10 mg. Peritrate (pentaerythritol tetranitrate) is a nitric acid ester of a tetrahydric alcohol (pentaerythritol).

Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: Peritrate (pentaerythritol tetranitrate), is indicated for the relief of angina pectoris (pain associated with coronary artery disease). It is not intended to abort the acute anginal episode but it is widely regarded as useful in the prophylactic treatment of angina pectoris. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg and Peritrate (pentaerythritol tetranitrate) are contraindicated in patients who have a history of sensitivity to the drug.

Warning: Data supporting the use of Peritrate (pentaerythritol tetranitrate) during the early days of the acute phase of myocardial infarction (the period during which clinical and laboratory findings are unstable) are insufficient to establish safety.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine, and many other agents.

Precautions: Should be used with caution in patients who have glaucoma. Tolerance to this drug, and cross-tolerance to other nitrates and nitrites may occur.

Adverse Reactions. Side effects reported to date have been predominantly related to rash (which requires discontinuation of medication) and headache and gastrointestinal distress, which are usually mild and transient with continuation of medication. In some cases severe, persistent headaches may occur.

In addition, the following adverse reactions to nitrates such as pentaerythritol tetranitrate have been reported in the literature:

- Cutaneous vasodilatation with flushing.
- Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop.
- An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration and collapse) can occur, even with the usual therapeutic doses. Alcohol may enhance this effect.

Dosage: Peritrate (pentaerythritol tetranitrate) may be administered in individualized doses up to 160 mg a day. Dosage can be initiated at one 10 mg or 20 mg tablet q.i.d. and titrated upward to 40 mg (two 20 mg tablets or one 40 mg tablet) q.i.d. one-half hour before or one hour after meals and at bedtime. Alternatively, Peritrate Sustained Action 80 mg can be administered on a convenient b.i.d. dosage schedule.

Supplied: Peritrate SA Sustained Action (pentaerythritol tetranitrate) 80 mg—double-layer, biconvex, dark green/light green tablets in bottles of 100 (N 0047-0004-51) and 1000 (N 0047-0004-60). Also unit dose, package of 10 x 10 strips (N 0047-0004-11).

Peritrate (pentaerythritol tetranitrate) 40 mg—pink scored tablets in bottles of 100 (N 0047-0008-51).

Peritrate (pentaerythritol tetranitrate) 20 mg—light green, scored tablets in bottles of 100 (N 0047-0001-51) and 1000 (N 0047-0001-60). Also unit dose, package of 10 x 10 strips (N 0047-0001-11).

Peritrate (pentaerythritol tetranitrate) 10 mg—light green, unscored tablets in bottles of 100 (N 0047-0007-51) and 1000 (N 0047-0007-60).

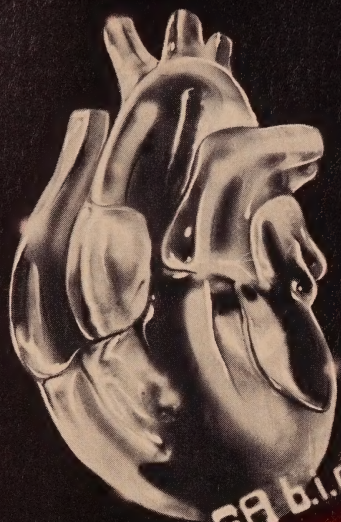
STORE BETWEEN 59° and 86° F (15° and 30° C).

Animal Pharmacology: In a series of carefully designed studies in pigs, Peritrate (pentaerythritol tetranitrate) was administered for 48 hours before an artificially induced occlusion of a major coronary artery and for seven days thereafter. The pigs were sacrificed at various intervals for periods up to six weeks. The result showed a significantly larger number of survivors in the drug-treated group. Damage to myocardial tissue in the drug-treated survivors was less extensive than in the untreated group. Studies in dogs subjected to oligemic shock through progressive bleeding have demonstrated that Peritrate (pentaerythritol tetranitrate) is vasoactive at the postarterial level, producing increased blood flow and better tissue perfusion. These animal experiments cannot be translated to the drug's actions in humans.

Full information is available on request.



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OPTIMUM

In many angina* patients, response to Peritrate is optimum when dosage is titrated to its maximum

Peritrate[®] SA Sustained Action
(pentaerythritol tetranitrate) **80 mg b.i.d.**

The simple aim of Peritrate prophylaxis* is to maintain adequate nitrate levels in the body so that fewer "breakthrough" angina attacks occur. To achieve this goal, many patients require maximum dosage—either Peritrate SA 80 mg b.i.d. or new Peritrate[®] 40 mg tablets q.i.d. Whichever form of Peritrate you choose, be sure you use it optimally. You can expect side effects to be few.

*This drug has been evaluated as possibly effective for this indication. See brief summary.

PE-GP-71

160 mg/day

however, no behavior problem, either at school or at home. He mastered all the academic tasks required at his grade level.

The reason this boy had been brought to me was that the family had recently moved, and the child was experiencing additional difficulties in relating to his peers. Careful history revealed that the boy's father and elder brother had gone through the same development up to age 10. They had both "matured more slowly" than the average individual, but had "caught up" afterwards.

Correct treatment for this boy's condition consisted of careful monitoring and emotional support for him and his family, and continued communication with the school.

Individuals who differ in their rate and pattern of development do not always fare so well as this boy because the environment, which is geared to the average individual, often acts on them traumatically, as you see from this case.

● *Case 2.* Jimmy, a 13-year-old boy, was involved in minor but repeated behavioral difficulties. His peers would call him names and antagonize him until he would lose his temper. He had very few friends; nevertheless, he enjoyed the warm acceptance of his family, including his siblings. He liked reading and was an outstanding student. His mother reported that Jimmy had been an unusually placid baby, happy to play by himself for hours. His grandfather and uncle were of similar psychologic make-up—shy and retiring to the point of avoiding any major social events, but well liked by their immediate families. Again, we reached the conclusion that we were not dealing primarily with an illness. Instead, the boy's

behavior represented a variation within the normal distribution curve of human characteristics. Because of its persistence and lack of development toward the average, however, it resulted in secondary troubles because of negative interaction with the environment. Treatment had to include some psychiatric work with the patient's reactions of frustration, as well as reassurance to the parents that they were on the right track in viewing their son as a "spitting image of his grandpa."

More clear-cut

Developmental (or maturational) lag is a more clear-cut and specifically definable condition because it means developmental retardation in certain mental areas while others, especially basic intelligence, develop normally. The areas most typically affected are nonverbal and verbal communication (especially various aspects of speech, perceptual and fine motor skills) and social interaction. You probably see many patients with this condition, for in view of today's expectations and pressure for early socialization and intellectual performance, parents and nursery school teachers are apt to notice these variations in preschoolers. Let me give an example.

● *Case 3.* When Mark was 4 years old, his nursery school teacher referred him to our child guidance clinic because she was concerned about his total lack of interaction with the other children. Moreover, the child had a habit of jumping about and posturing rather than talking. Speech had started barely half a year earlier and, at the time of referral, the boy used mainly short sentences and baby talk. The parents themselves ex-

pressed no concern, however, largely because this rate of development was not unusual within their families. Even though our clinical picture indicated hyperactivity syndrome in addition to developmental lag, we did not recommend treatment, since the parents were not concerned and the child was not disruptive at the nursery school. Instead, we urged the parents to report to us regularly about the child's progress.

Hyperactivity's role

● *Case 3 continued.* A year later, Mark's situation was largely the same, with the notable exception that his short attention span and somewhat low frustration tolerance were more in evidence and he was starting to be disruptive both at home and at school. We decided that the hyperactivity component had now "crystallized" and needed treatment.

"If you do not do something about it, perhaps nobody else will, until later—perhaps too late."

The child responded to methylphenidate with moderate improvement in attention span and frustration tolerance, but his lack of interaction and his posturing continued. The improvement in his concentration encouraged learning, however, and improvement in the frustration tolerance helped in his socialization, and his rate of development was slightly increased. At age 6, he is still an extremely shy child who barely interacts with peers and rarely even plays with toys that are not his or his brother's. He still has a stilted vocabulary and worries his teacher because of his "differentness," but he continues to progress and

WHEN VITAMIN DEFICIENCY IS PART OF THE PICTURE



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Vitamin B₁ (thiamine mononitrate) 25 mg
Vitamin B₂ (riboflavin) 15 mg

Vitamin B₆ (pyridoxine HCl) 10 mg
Vitamin B₁₂ (cyanocobalamin) 5 mcg
Nicotinamide (niacinamide) 100 mg
dl-Panthenol 20 mg

now trusts certain people, such as his teachers and me.

Mark's case illustrates several points. Developmental lag and hyperactivity often coexist. Indeed, developmental lag is often thought to be the neurophysiologic basis for hyperactivity. Yet the treatment is not quite the same. Developmental lag calls for a combination of the treatment approaches to all three conditions: support, understanding, and enlightenment as to the environmental factors; careful monitoring of the rate of educational progress, for developmental lag is often reflected in specific learning disorders; and pharmacotherapy with stimulants or, more rarely, tranquilizers for the associated hyperactivity syndrome.*

Treatment

All three conditions—constitutional variations in temperament, developmental lag, and hyperactivity—can be treated provided the family and the educators are cooperative. Another provision is that the child should not have developed significant feelings of inferiority with the resulting psychologic defenses of a "chip-on-the-shoulder" attitude or over-aggressiveness, or withdrawal. If he has, psychiatric consultation is indicated.

Temperament variations

Temperament variations can be diagnosed from a frequent family history, adequate functioning, and the absence of significant psychopathology, specific learning disorder, and symptoms of hyperactivity. You need to know the developmental landmarks and usual problems of normal children. Treatment consists of telling the parents the child has

no disease, yet urging them to keep their eyes open for trouble from interaction with the environment, and stressing that they must allow you to monitor the child's status at regular intervals, say every 6 months, and notify you sooner if social or learning difficulties arise.

Deal with developmental lag

Developmental lag calls for greater activity on your part. You need to check whether someone is attending to the speech and learning difficulties so frequently present, because schools are not always quick enough to spot or deal with them. Advise the parents to insist that the school system give their child his rightful care. Also, see that someone attends to the child's social difficulties. For the child who is frustrated because he is not equal to his peers in skills and poise, someone must find areas of strength where he can hold his own. Have the parents and the school system (or camp or social group leader) protect the child against excessive frustration and abuse, for a "fear of overprotectiveness" can be harmful here.

Hyperactivity, too

You need to watch out for the development of an associated hyperactivity syndrome with its definite triad of easy distractibility, low frustration tolerance, and hypermobility. This syndrome requires additional treatment. Moreover, you must decide when the child's emotional reactions to the disharmony between his development and that of his environment reach a level of intensity and persistence that call for psychiatric consultation. If you do not do something about it, perhaps nobody else will, until later—perhaps too late.

Tablets

Percodan® II

DESCRIPTION Each yellow, scored tablet contains 4.50 mg. oxycodone HCl (WARNING: May be habit forming), 0.38 mg. oxycodone terephthalate (WARNING: May be habit forming), 254 mg. aspirin, 160 mg. phenacetin, and 32 mg. caffeine.

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone, aspirin, phenacetin or caffeine.

WARNINGS **Drug Dependence** Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCODAN®, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCODAN® is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCODAN® should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCODAN® may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCODAN® should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCODAN® should not be administered to children.

Salicylates should be used with caution in the presence of peptic ulcer or coagulation abnormalities.

PRECAUTIONS **Head injury and increased intracranial pressure** The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCODAN® or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCODAN® should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

Phenacetin has been reported to damage the kidneys when taken in excessive amounts for a long time.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation and pruritus.

DOSEAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCODAN® may be additive with that of other CNS depressants. See WARNINGS.

DEA Order Form Required.

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*Fras, Ivan: The "real" hyperactive child. *Consultant*, Vol. 15, No. 7, pp 97-103, 1975.

New interest in sclerotherapy for varicose veins

Ronald Dee, M.D.

The patient's varicose veins have continued to cause aching and swelling despite the fact that he is using supportive stockings. What comes next?

Until recently, the answer would surely have been a recommendation for surgical stripping of the diseased veins. After all, so it is generally believed, sclerotherapy was tried many years ago and found to be unsatisfactory. Some physicians put it more bluntly: "Sclerotherapy is a dangerous procedure which can cause thrombophlebitis and pulmonary embolism."

True, in the wrong hands sclerotherapy can do more harm than good. About the only con-

sideration many physicians give it anymore is as a secondary measure to treat varicosities that persist after a vein stripping. However, venous stripping is not without its limitations. The operation can be painful, incapacitating, or ineffective, to say nothing of the need for hospitalization, operating room, and anesthesia. The resurgence of interest in sclerotherapy grew out of the need for a procedure that could be done outside the hospital.

Fegan and Henry in Dublin used sclerotherapy to treat the varicose veins in persons who, because of a shortage of hospital beds, could not be treated by vein stripping. The procedure worked in a very large number of patients. The Irish physicians were successful where others had failed because they discovered the causes of previous failures and worked out ways to prevent them.

My purpose is to go over our technique of sclerotherapy, show its indications and contraindications, and reassess its place in the treatment of varicose veins.

The aim of therapy

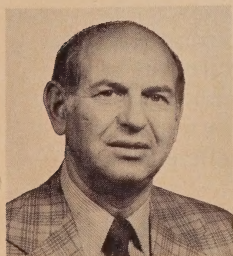
Sclerotherapy means treatment that causes hardening. The sclerosing agent irritates the wall of the vein and sets off the changes that give venous fibrosis. The treatment is based on the theory that varicosities re-

sult from valvular incompetence in one or more of the perforating veins of the lower leg (Box). When the person with varicosities walks, his calf muscles contract and eject blood from the deep veins out through the incompetent perforating veins. Sealing off the superficial veins at these sites protects them from the high-pressure leaks and corrects the cause of the varicosity.

Injection technique

Improvements in how to give sclerotherapy are responsible for its success. The technique can be readily learned, but you should not try it without some experience in very firm compression bandaging.

- *Selecting injection sites.* Before the injection the patient should stand so that the physician can palpate each varicosity throughout its length and mark its course on the skin (Figure 1). The patient then lies on his back on the examining table. He raises his leg so that his heel rests on the physician's shoulder. By careful palpation along the course of the veins, the physician may find one or more depressed areas. These places are sometimes tender, and they usually coincide with openings in the deep fascia that have been widened by dilated perforating veins. He should mark each of these places separately. Fingertip pressure applied to one or



Dr. Dee is assistant clinical professor of surgery at Albert Einstein College of Medicine, New York, and attending surgeon at United Hospital, Port Chester. He is visiting surgeon at Jacobi Hospital in the Bronx and is responsible for the varicose veins clinic there. Dr. Dee is a diplomate of the American Board of Surgery and a fellow of the American College of Surgeons.

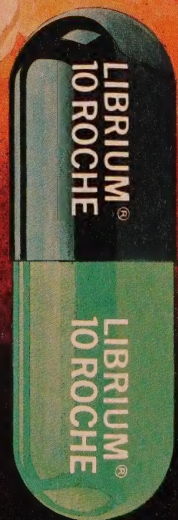
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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported.

Usage in Pregnancy: Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.

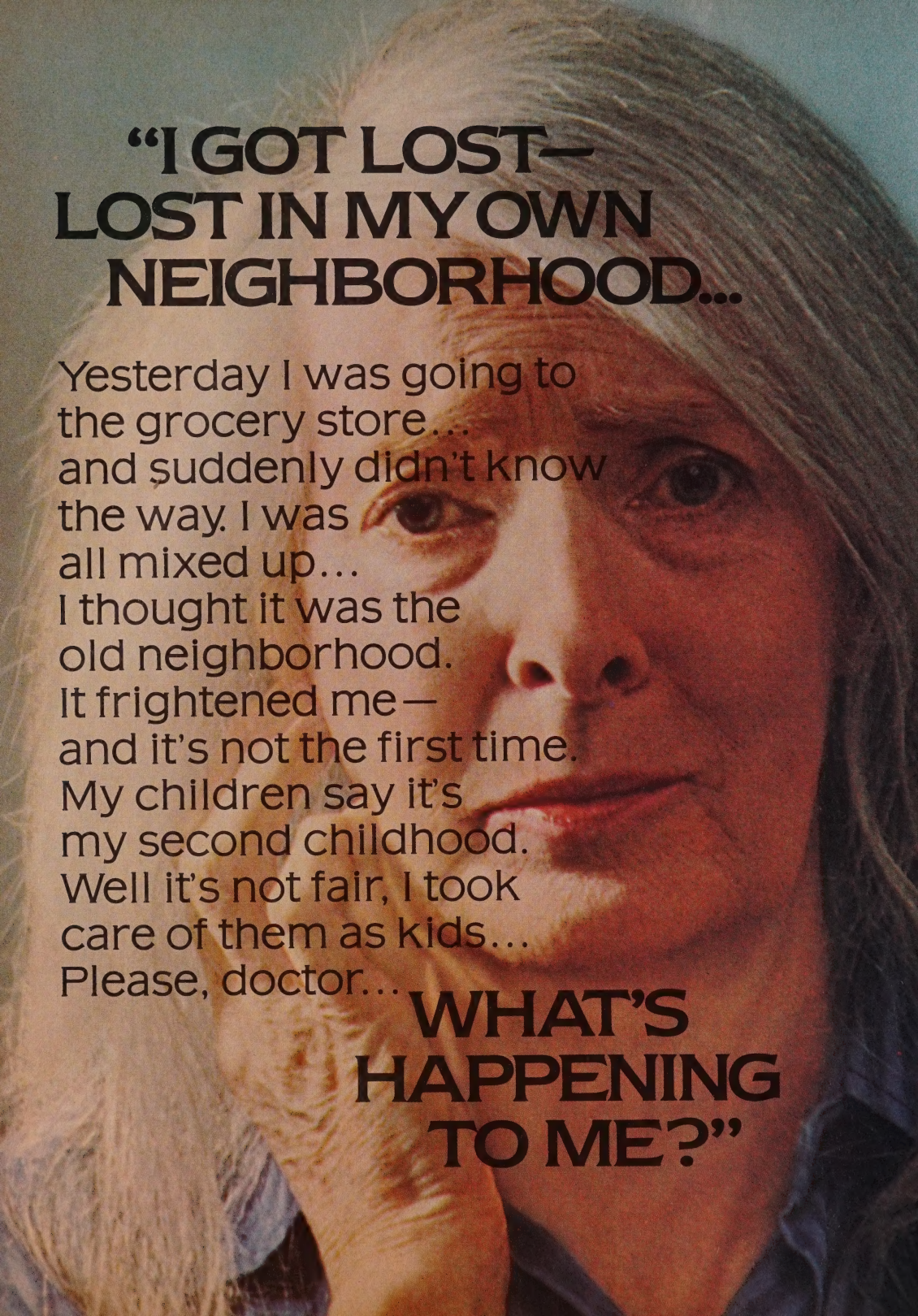
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

Supplied: Librium® Capsules containing 5 mg, 10 mg or 25 mg chlordiazepoxide HCl. Libritabs® Tablets containing 5 mg, 10 mg or 25 mg chlordiazepoxide.



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“I GOT LOST— LOST IN MY OWN NEIGHBORHOOD...”

Yesterday I was going to
the grocery store...
and suddenly didn't know
the way. I was
all mixed up...

I thought it was the
old neighborhood.
It frightened me —
and it's not the first time.

My children say it's
my second childhood.
Well it's not fair, I took
care of them as kids...

Please, doctor...

WHAT'S HAPPENING TO ME?”

WHEN "GRAY AREA" SYMPTOMS START TO AFFECT THE ELDERLY PATIENT'S LIFE

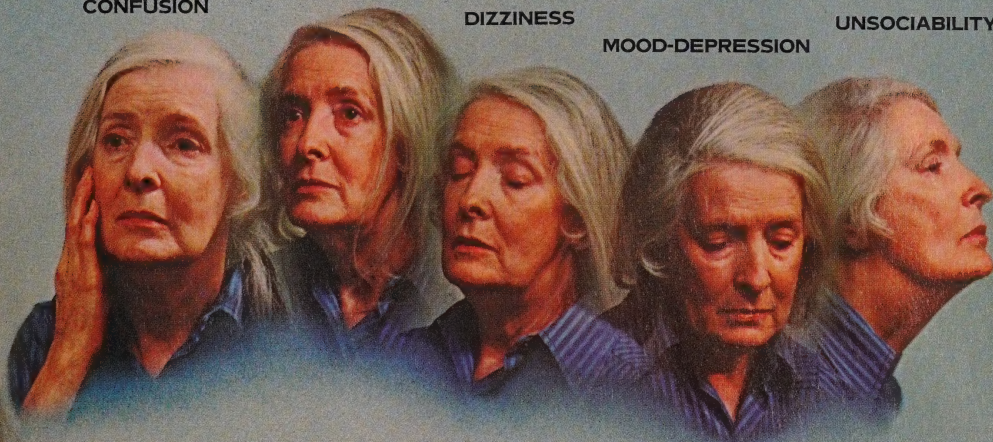
CONFUSION

LACK OF SELF-CARE

DIZZINESS

MOOD-DEPRESSION

UNSOCIABILITY



The elderly patient with "gray area" symptoms may not always be aware of these early and subtle changes... or able to articulate them. But the patient may be humiliated and hurt by the inability to control confusion, lack of self-care, dizziness, mood-depression, and unsociability... problems that can alienate patient from family, from friends, and even from self.

Hydergine therapy can often bring these patients meaningful help. Given early — when symptoms are still mild to moderate — Hydergine therapy may retard or improve "gray area" symptoms.

TO HELP RELIEVE
"GRAY AREA" SYMPTOMS

HYDERGINE[®] Sublingual
Tablets. **1 mg**

GIVE ENOUGH, SOON ENOUGH,
LONG ENOUGH

For Brief Summary, please see following page.



R_x

*Hydergine 1mg.
Sublingual Tablets #50
Sig: Tab $\dot{\bar{i}}$ tid
dissolved under tongue*

dispense as written

M.D.

A Simple Regimen
Where Simplicity Counts

A SINGLE 1-mg HYDERGINE SUBLINGUAL TABLET THREE TIMES A DAY

- Meets the proper 3-mg total daily dose of Hydergine therapy.
- Makes compliance easier for patients who might be confused by more complicated schedules.
- Helps assure optimal dosage because of better adherence to dosage regimen.
- Oval shape of 1-mg tablet makes it easier for the elderly patient to identify.

Contraindications: Hypersensitivity to the drug.

Precautions: *Because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing Hydergine sublingual tablets.*

Adverse Reactions: Serious side effects have not been found. Some sublingual irritation, transient nausea, and gastric disturbances have been reported. Hydergine sublingual tablets do not possess the vasoconstrictor properties of natural ergot alkaloids.

Dosage and Administration: 1 mg sublingually three times daily. Alleviation of symptoms is usually gradual and results may not be observed for 3-4 weeks.

WHEN "GRAY AREA" SYMPTOMS START TO
AFFECT THE ELDERLY PATIENT'S LIFE

HYDERGINE[®] Sublingual
Tablets. **1mg**

Each 1-mg Hydergine sublingual tablet contains dihydroergocornine 0.333 mg, dihydroergocristine 0.333 mg, and dihydroergokryptine 0.333 mg, (Dihydro-alpha-ergokryptine and Dihydro-beta-ergokryptine in the proportion of 2:1) as the mesylates, representing a total of 1.0 mg

How varicose veins happen and why

Four-legged animals do not have varicose veins because the vena cava runs horizontally and this evens out the pull of gravity. However, the upright stance of humans is a different matter. Gravity exerts its pull on the column of blood, and every Valsalva maneuver increases intra-abdominal pressure. Blood pressure is of little help in pushing venous blood back to the heart; the system depends on a set of one-way valves and the pumping action of skeletal muscles.

Veins in the leg

The lower limb contains three groups of veins:

1. *Superficial veins* lie in the subcutaneous tissues. They contain valves that keep blood flowing toward the heart.

2. *Deep veins* are found within the deep fascial compartment of the leg. There are two types of deep veins.

- *The venae comitantes* are paired vessels in the calf. They drain into the popliteal and femoral veins.

- *The intramuscular veins* are sinusoidal vessels within the gastrocnemius and soleus muscles. They drain into the venae comitantes.

3. *Perforating veins* are short vessels that perforate the deep fascia to join the superficial and deep veins. Their valves direct the flow of blood from the skin to the deep veins. The exception is the foot, where blood flows from the deep veins to the surface. The long and short saphenous veins penetrate the deep fascia before joining the deep system and they themselves end as perforating veins.

How blood returns from the foot

During walking, a person applies his body weight to his feet. The weight compresses the deep veins in the foot and sends blood to the surface, where it flows upward to the superficial veins of the leg. Meanwhile, the calf contracts and squeezes the deep veins of the leg. Valves send the blood cephalad toward the popliteal and femoral veins—and keep it from leaking outward through the perforating veins to the superficial veins. Raising the foot for the next step relaxes the calf. Blood leaves the superficial veins and flows through the perforating veins to the deep

veins. The foot strikes the ground again and the cycle is repeated.

The why of varicose veins

Venous drainage works best when the person is walking, or when his legs are raised above the horizontal level. Standing still for long periods thus favors the development of varicose veins, and so does an obstruction that impedes venous flow. Two theories have been proposed to explain varicose veins:

- *"Above-down" theory.* Proponents of this theory believe that the problem begins in the valves of the long saphenous vein at its junction with the femoral vein. Hydrostatic pressure of the column of blood causes blood to reflux into the long saphenous veins. Incompetent, the vein distends and renders the valves distal to it incompetent. The disease progresses downward to involve tributaries as well as perforating veins. The "above-down" theory can explain varicose veins that develop from a pelvic or abdominal obstruction to venous flow. However, varicosities rarely occur in the thigh without leg involvement, though the reverse is often the case.

- *Perforating vein theory.* A more likely explanation for varicose veins is that the valvular incompetence begins in one or more of the perforating veins in the leg. Perhaps the defect is inherited or caused by minor trauma. Anyway, the valves give way under stress and let blood leak from the deep veins to the superficial ones. Once the perforating vein valves begin to leak, contraction of the calf muscles ejects blood under a high pressure to the surface veins. High-pressure blood flow causes the muscle in the wall of the superficial vein to hypertrophy. Later the vein distends, and eventually it dilates so much that its valves become incompetent. Reflux occurs in the superficial veins, and spreads to other veins. Early in the disease, the valve cusps are functionally incompetent, but the condition is reversible. It is not necessary to remove these veins by surgery—or to obliterate them completely by sclerosis. The goal of injection therapy is to seal off high-pressure leaks through the perforating veins and thus correct the varicosities by removing their cause.

two of these spots while the patient stands will allow the examiner to prevent retrograde filling of some or all of the previously marked veins. The sclerosing agent should be injected at each place where pressure prevents retrograde filling of the vein. About 60% of the time the injection site is where a perforating

vein enters the superficial vein. However, perforating veins that are missed during the first treatment can be injected at a subsequent visit. The rule is to inject no more than four or five sites at a time.

- *The sclerosing agent.* The agent of choice is 3% sodium tetradecyl sulfate. Within sec-

onds it begins to exert its effect on the protein of the venous intima, and at the dosage used it is inactivated by plasma and does not cause blood coagulation. The solution is rapidly washed away by the deep venous flow from the leg.

- *Needle insertion.* The injection is given through a 25-gauge,



Figure 1 — Varicose veins in the left calf.



Figure 2 — Syringes and needles in place for injection.



Figure 3 — Compression on either side of the needle closes off that part of the vein during the injection.



Figure 4 — Sponge over the injection site is held tightly by tape or a Velcro bandage.



Figure 5 — An Unna bandage is applied without tension.



Figure 6 — An elastic adhesive bandage is wrapped around the leg tightly enough to compress the superficial veins. Then a stockinet is pulled over the leg and the procedure is completed.

½-inch needle with a tuberculin syringe. The patient stands while a needle is inserted into the vein at each of the chosen sites. The tuberculin syringe, containing 0.5 ml of sodium tetradecyl sulfate, is taped to the skin. No injection is made at this time.

- **Leg elevation.** The patient then assumes a supine position with his leg elevated on a high stand (Figure 2). This empties the vein of blood, and makes it easier to keep the walls of the vein closed after the injection. Two fingers are spread apart and pressed above and below the needle during the injection (Figure 3). The pressure occludes this segment of the vein during the 30 seconds needed for the slow injection.

- **The dressing.** A plastic foam sponge is taped over each injection site, with gauze beneath it to prevent a contact allergic reaction (Figure 4). A bandage is applied very firmly from the base of the toes to a few inches above the highest injection site (Figure 5).

Importance of compression

The original technique for sclerotherapy did not include compression of the vein following the injection. The agent was simply injected and the puncture site was covered with a piece of gauze. Thrombophlebitis soon developed in the injected vein, and the final outcome was unpredictable. Sometimes the vein would undergo fibrosis. Other times the clot would retract and allow recanalization; the patient's varicosities would be worse than before the injection. Formation of a large clot caused another worry. It could extend into the deep veins and break loose to cause pulmonary embolism—though this probably

happened no more often than after vein stripping.

Compression of the vein after the injection prevents a large clot from forming (Figure 6). The pressure pushes the walls of the vein together so that fibrosis can fuse the opening completely. The chance of recanalization or of extension of the clot to the deep veins is minimized.

Dr. Fegan recommends 6 weeks of compression after the injection, but we have found that 3 weeks is adequate for most patients.

Continued walking

A compression bandage does not keep the patient from walking. In fact, he should walk a block or so before driving home, and then walk 2 to 3 miles a day. Walking encourages blood to flow through the unoccluded veins.

Follow-up care

The patient should keep his legs elevated when sitting for long periods. He should be told that he may have some burning sensation in the injected leg on the night of treatment or for a night or two afterwards. Walking and aspirin therapy will relieve the pain.

After 1 week the bandages should be removed and the leg examined. Residual varicose veins from missed perforating veins can be injected. The compression bandage goes back on exactly as before, and is removed after 2 more weeks.

The patient is told that the bandage must not be removed except by the treating physician, and it must not be allowed to get wet. Bathing is a problem; however, a large plastic bag over the bandaged leg, secured above the bandage, enables showering.

Tender nodules that can be

felt along the course of the injected vein may be due to sequestered blood. The blood should be evacuated with an 18-gauge needle and gentle pressure. A small dressing may suffice, but if the nodule was large it may be wise to continue the compression bandage for an extra week.

An injection high in the leg might be necessary, but sometimes adequate compression of the thigh by a bandage is not possible if the patient is obese. It may be necessary to ligate this patient's thigh vein after completing injection therapy of the lower part of the leg. The long saphenous vein and its tributaries can be tied at the groin under local anesthesia. The patient can walk immediately after the surgery. Venous stripping has not been necessary in any of our patients.

Indications for sclerotherapy

Presence of varicose veins is not an indication for treating them, nor is the absence of symptoms a reason for refusal. Indications for injection therapy include:

- **Aching, tiredness, and pain** in the legs after prolonged standing, especially if the patient gets relief from elevating his legs or wearing support hose. Some patients with varicose veins have night cramps, and arterial insufficiency and other causes of the cramps should be excluded before attributing the cramps to the varicosities.

- **Cosmetic reasons**, so long as the patient understands that appearance alone is not a medical reason for treatment. Women who have been refused surgery because of their minimal disability may be anxious to have sclerotherapy. Successful treatment of the varicosities allows the woman to swim, play tennis, and engage in other activities she

has passed up because of her varicosities.

- *Past history of phlebitis* is a reason for sclerotherapy, but the potential danger of phlebitis is not. Superficial thrombophlebitis is rarely dangerous; embolization is unlikely because of the firm attachment of the thrombus to the vessel wall.

- *Leg ulceration* may be an indication for treatment. After the varicosities are treated, the patient should wear firm support hose. The support hose is better for long-term therapy than bandaging the leg, since a patient-applied bandage may compress the calf and produce a venous tourniquet.

Contraindications

The patient should have a thorough examination before his veins are injected in order to make sure that varicosities have caused his symptoms, and that he does not have some other disease. For example, the leg pain may represent intermittent claudication or sciatica, or arthritis of the knee or hip. Sclerotherapy is contraindicated if the patient has active superficial thrombophlebitis, a blood dyscrasia, tumor, thyrotoxicosis, or any condition requiring more urgent therapy. Injection of varicosities is not indicated if the patient is bedridden.

Tenderness in a varicose vein is usually attributed to phlebitis. A small tender nodule may in fact be a lipoma or neurofibroma. An obese person may have panniculitis with diffuse subcutaneous tenderness. Then tenderness occurs in all parts of the leg, not just the varices. Sclerotherapy would not help the patient with panniculitis, nor could the person tolerate the compression bandage.

Women taking birth control

pills have an increased risk of forming a blood clot. For this reason, the woman should stop the Pill at least 6 weeks before injection therapy. Sclerotherapy should not be used during the first trimester of pregnancy, and should be given only in the later stages of pregnancy if the veins are very painful and are not controlled by support stockings.

Possible complications

Before giving sclerotherapy, the physician should explain the procedure and its possible complications. An allergic reaction to sodium tetradecyl sulfate can occur—though it is rare. An allergic reaction should not be confused with toxicity from an overdose of the sclerosing agent, which can be prevented by using a total of no more than 3 to 4 ml of sodium tetradecyl sulfate during one treatment.

Although it is more difficult for them to bathe, some patients ask for both legs to be treated at the same time. When they do, be careful not to exceed a total dose of 4 ml of a 3% solution.

Deep vein thrombosis and pulmonary embolism are quoted as dangers of injection therapy. In fact, the incidence of deep vein thrombosis is .08%, and no fatalities were reported in a series of several thousand cases treated by this method. The incidence of deep vein thrombosis is lower than that following surgery on the leg veins.

Injection or leakage of sodium tetradecyl sulfate outside the vein can cause necrosis of the subcutaneous tissue and skin. The ulcer will take several weeks to heal, and may leave a scar like a vaccination mark. Even after routine sclerotherapy, brown staining may appear in the skin above the injection site. The pigmentation may be permanent,

but it usually subsides after several weeks or months. Warn the patient ahead of time about the possibility of pigmentation if he is having sclerotherapy for cosmetic reasons. Forewarned patients are less likely to be displeased by the appearance of the brown spot.

Results of treatment

Good to excellent results are achieved in more than 80% of patients who request sclerotherapy for cosmetic reasons. Symptomatic relief in patients whose treatment was primarily for pain or aching was achieved in more than 95% of cases. Patients who are not satisfied with the initial cosmetic results may be improved with further treatment.

The question of recurrences is often raised. Varicose veins cannot be cured whatever treatment method is used, and the patient may develop new varicose veins in the future. The patient must understand this before the treatment. A yearly return visit is a must so that the physician can locate new varices and treat them before they become large. Only 1 or 2 weeks of compression are necessary if the veins are treated early. Patients who have recurrences following a vein stripping are usually reluctant to undergo further surgery. Yet, the patient who has had injection therapy may notice a new varicose vein and request further therapy.

In conclusion, a properly applied bandage after injecting an empty vein has greatly improved the results of sclerotherapy. Casual use of the procedure gives seemingly good results in the early stages because of obliteration of the vein by thrombosis, but recanalization is common. In the right hands injection therapy can be gratifying for the patient and the physician.



Cu-7® (brand of intrauterine copper contraceptive)

Description: The plastic component of the Cu-7 is composed of pharmaceutical grade polypropylene homopolymer with barium sulfate added to render it radiopaque. Its shape approximates the number 7; it is substantially smaller than previously available intrauterine devices.

Coiled around the vertical limb is a pure, virgin electrolytic copper wire providing 200mm² of exposed copper surface area. A polypropylene retrieval thread is fastened to the free end of the vertical limb of the Cu-7.

The Cu-7 is supplied with a simple tubular polypropylene inserter. All components are sterile.

Pharmacology: Available data indicate that the contraceptive effectiveness of the Cu-7 is enhanced by a minute quantity of copper released continuously from the coiled copper into the uterine cavity.

The exact mechanism by which metallic copper enhances the contraceptive effect of an IUD has not been conclusively demonstrated. Various hypotheses have been advanced; the most common being that copper placed in the uterus interferes with enzymatic or other processes that regulate blastocyst implantation.

Animal studies suggest that copper may play an additional role by reduction of sperm transport within the uterine environment.

Indication and Usage: Prevention of pregnancy. The Cu-7 is one of several safe and effective methods of contraception which may be considered for a particular patient.

Different event rates have been reported with the use of different intrauterine contraceptives. Inasmuch as these rates are usually derived from separate studies conducted by different investigators in several population groups, a comparison cannot be made with precision. Even in different studies with the same contraceptive, considerably different rates are likely to be obtained because of differing characteristics of the study population. Furthermore, event rates per unit of time tend to be lower as clinical experience is expanded, possibly due to retention in the clinical study of those patients who accept the treatment regimen, not having discontinued due to adverse reactions or pregnancy, so that those remaining in the study were those less susceptible. In clinical trials of the Cu-7 conducted by Searle Laboratories, use effectiveness was determined as follows for parous and nulliparous women, as tabulated by the life table method. (Rates are expressed as cumulative events per 100 women through 12, 24, and 36 months of use.)

This experience encompasses 403,427 woman-months of use, including 12 months for 12,013 women, 24 months for 8,505 and 36 months for 3,940.

	12 Months		24 Months		36 Months	
	Parous	Nulliparous	Parous	Nulliparous	Parous	Nulliparous
Pregnancy	1.9	1.6	2.9	2.5	3.3	3.3
Expulsion	5.7	8.0	6.8	9.2	7.3	9.6
Medical removal	10.6	13.7	18.0	20.7	24.3	28.4
Continuation	75.0	68.3	52.8	49.2	26.4	19.9

Contraindications: The presence of any of the following at the scheduled time of insertion constitutes a contraindication: pregnancy or suspicion of pregnancy, significant anemia, abnormalities of the uterine cavity, acute pelvic inflammatory disease or a history of repeated pelvic inflammatory disease, postpartum endometritis or infection within the past three months, previous ectopic pregnancy, endometrial or cervical disease such as hyperplasia or carcinoma, unexplained vaginal bleeding until cancer has been ruled out, acute cervicitis, and a known or suspected allergy to copper.

Warnings: **A. Pregnancy:** (1) **Septic abortion:** Reports have indicated an increased incidence of septic abortion associated in some instances with septicemia, septic shock and IUD in situ. Under such circumstances, the Cu-7 should be removed, appropriate bacteriological studies done, and appropriate antibiotic treatment instituted. If pregnancy should occur with a Cu-7 in situ, the Cu-7 should be removed if the string is visible or, if removal proves to be or would be difficult, interruption of the pregnancy should be considered and offered as an option. If the patient elects to maintain the pregnancy and the Cu-7 remains in situ, she should be warned that there may be an increased risk of sepsis and she should be followed with vigilance.

(2) **Ectopic pregnancy:** A pregnancy which occurs while a patient is using an IUD is more likely to be ectopic in nature. Therefore, such patients who become pregnant should be carefully evaluated for this possibility.

B. Severe pelvic infection: Occasionally, serious pelvic infection which is unresponsive to treatment may occur with an IUD in situ. Under such circumstances, the Cu-7 should be removed, appropriate bacteriological studies done, and appropriate antibiotic treatment instituted.

C. Perforation: Perforations of the uterus have occurred, usually during insertions into patients sooner than two months after abortion or delivery. If penetration into the abdominal cavity occurs, laparotomy or laparoscopy should be performed as soon as medically indicated and the Cu-7 removed. Local inflammatory reaction with abscess formation is a possibility if the Cu-7 is left in the abdomen. Cervical perforations, often asymptomatic, have also been reported. If these occur, the device should be removed.

D. Microwave therapy: The use of microwave therapy in a patient with a metal-containing prosthesis may cause heat injury to the surrounding tissue. Therefore, microwave therapy to the abdominal and sacral areas should not be used on patients using a Cu-7.

E. Copper effects: Additional amounts of copper available to the body from the Cu-7 may precipitate symptoms in women with undiagnosed Wilson's disease. The incidence of Wilson's disease is 1 in 200,000. The long-term effects on the offspring

of the presence of copper in the uterus during pregnancy are unknown.

Precautions and Routine Examinations: A. Patient examination: The physician should determine that the patient is not pregnant. A pelvic examination and gonorrhea culture should be done. The possibility of insertion in the presence of an existing undetermined pregnancy is reduced if insertion is performed during the latter part of the menstrual period or one or two days thereafter. The Cu-7 should not be inserted post partum or post abortion until involution of the uterus has been completed. Sound the uterus prior to insertion and exercise care to avoid perforation. Do not use excessive force. It is, however, necessary to place the Cu-7 as high as possible within the uterine cavity to help avoid downward displacement or expulsion that could result in a pregnancy.

Since the Cu-7 represents a different design in intrauterine contraception, physicians are cautioned that it is imperative for them to become thoroughly familiar with the instructions for use before attempting placement of the Cu-7.

B. Requirements for continuation and removal: (1) The Cu-7 must be replaced before the end of the third year of use. There is no evidence that contraceptive efficacy decreases with time in up to three years of use. The contraceptive effectiveness after three years has not been established; therefore, the patient should be informed of the known duration of contraceptive efficacy and be advised that the Cu-7 should be removed in three years.

(2) The Cu-7 should be removed for the following medical reasons: menorrhagia and/or metrorrhagia producing anemia, uncontrolled pelvic infection, intractable pain often aggravated by intercourse, dyspareunia, pregnancy, if the string is visible, endometrial or cervical malignancy, uterine or cervical perforation, or any indication of partial expulsion.

(3) If the retrieval thread cannot be visualized it may have retracted into the uterus or have been broken off, or the Cu-7 may have been expelled. Localization usually may be made by feeling with a probe; if not, x-ray or sonography can be used. When the physician elects to recover a Cu-7 with the thread not visible, the removal instructions should be considered.

C. Continuing care of patients: (1) Patients should be reexamined and evaluated within three months after Cu-7 insertion.

(2) Routine annual examination with appropriate medical and laboratory evaluation should be carried out.

(3) If any patient with a Cu-7 suddenly develops overt clinical hepatitis or abnormal liver function tests, appropriate diagnostic procedures should be initiated.

(4) The patient should be told that some light bleeding or cramps may occur during the first few days after insertion, but if these symptoms continue or are severe she should report to her physician. She should be instructed on how to inspect periodically to make certain that the thread still protrudes from the cervix and cautioned that there is no protection if the device has been expelled. She should also be cautioned not to displace the Cu-7 by pulling on the thread, and to return within three years for removal of the Cu-7 and replacement if desired.

(5) A report has appeared in the literature suggesting that a copper-induced urticarial allergic skin reaction developed in a woman using a copper IUD. If symptoms of such an allergic response occur the patient should be instructed to tell the consulting physician that a copper-bearing device is being used.

Adverse Reactions: Perforations of the uterus and cervix have occurred. Perforation into the abdomen has been followed by abdominal adhesions, intestinal perforation, intestinal obstruction, and inflammation and erosion of adjacent viscera. Pregnancy has occurred with the Cu-7 in situ when the Cu-7 has been partially or completely expelled.

The incidence of spontaneous abortion, when conception occurs with intrauterine devices in situ, appears to be increased over that in unprotected women. Insertion cramping, usually of no more than a few seconds duration, may occur; however, some women may experience residual cramping for several hours or even days. Intermenstrual spotting or bleeding or prolongation of menstrual flow may occur in the first few cycles. Uncommonly, pelvic infection has been reported. Complete or partial expulsion may sometimes occur, particularly in those patients with uteri measuring less than 6.5 cm by sounding. The following complaints have also been reported with IUDs although their relation to the Cu-7 has not been established: amenorrhea or delayed menses, backaches, cervical erosion, cystic masses in the pelvis, vaginitis, leg pain or soreness, weight loss or gain, nervousness, dyspareunia, cystitis, endometritis, septic abortion, septicemia, leukorrhea, ectopic pregnancy, difficult removal, uterine embedding, anemia, pain and bradycardia and syncope secondary to insertion.

Dosage and Administration: The Cu-7 is to be placed in the uterine cavity.

The small diameter of the Cu-7 facilitates easy insertion in nulligravidae and nulliparous, as well as parous women. The optimal time of insertion is during the latter part of the menstrual flow or one or two days thereafter. The cervical canal is relatively more patent at that time, and there is little chance that the patient may be pregnant.

Present information indicates that efficacy is retained for 36 months, until adequate data indicating a longer effective life become available, the Cu-7 must be removed within 36 months from the date of insertion and a new one inserted if desired. If partial expulsion occurs, removal is indicated, and a new Cu-7 may be inserted. Removal of the Cu-7 may also be indicated in the event of heavy or persistent bleeding.

The physician should become thoroughly familiar with the instructions for use before attempting insertion or removal of the Cu-7.

How Supplied: Available in cartons of 6 and boxes of 30 and 100 sterile units (Cu-7 with an inserter) and sufficient patient information cards.

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Coping with common back problems

Most patients with back pain can be helped by bed rest, muscle relaxants, and mild exercise. Those who are not, probably have more complicated problems.

Jack Waxman, M.D.

The human lumbar spine is not really adapted to our way of life. As a result, it often degenerates more quickly than the rest of the body, causing a multitude of ills. These ills include ligamentous and muscular strain, disk fragmentation and protrusion, spur formation, and apophyseal osteoarthritis. Each event brings much pain and spasm, which may be radicular, and managed by long-term bed rest, in or out of the hospital. But that is economically impractical. Bed rest also adds to the patient's sense of dependence, it weakens muscles and bones, and it heightens the risk of thrombi and embolisms.

For all these reasons, being able to rest the spine while the patient is in an upright position is a good thing. It permits the patient to heal as he continues working. It is feasible as long as progressive neurologic loss does not occur, and so long as the initial, severe pain subsides promptly after a few hours or days of bed rest, and does not recur when the patient arises. Some patients have low pain tolerance, or excessive anxiety and subsequent muscle spasm, and they need prolonged bed rest. But most patients need only an

occasional hour or two of rest each day in bed or on the floor.

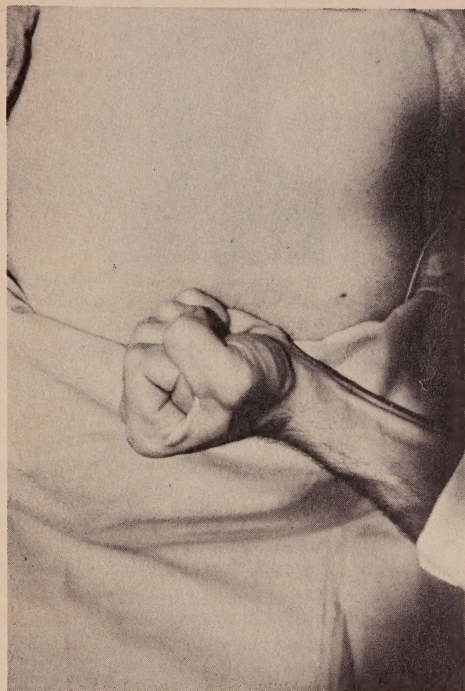
Before you advise this therapy, of course you should be sure you are dealing with a back sprain or mild disk problem. You must rule out such conditions as radicular syndromes. Also, if the patient does not respond to this program, or if neurologic signs (including weakness and numbness) appear and worsen, refer him to a neurosurgeon or an orthopedic surgeon.

How to check

Radicular syndromes need careful observation to prevent permanent muscle weakness and sensory loss. Suspect radicular problems if:

- The pain is unilateral.
- Pain or tingling occurs at least as distal as the lower buttock crease or lateral thigh.
- The straight-leg-raising test, particularly in the sitting position, causes pain in the back or the buttocks, but not in the thigh or the leg. (When the leg is lowered slightly, the pain diminishes, and then recurs when the ankle is dorsiflexed.)
- A small patch of paraspinal numbness (perhaps only about 2 inches in length) appears on the affected side.

Do lumbar percussion. (Fig-



Figure—The patient should lean forward during percussion.

ure). During percussion of the lumbar spine the patient should be seated and leaning forward. Spinous process motion confirms local percussion tenderness. Now use your thumb and index finger and rather forcibly lean on the back. Then press both thumbs simultaneously along paraspinal regions and ask the patient to indicate which muscles are sore. These maneuvers confirm the degree of pain and the level of the lumbar syndrome, but are not specific for any one diagnosis.

Initial evaluation also includes a check for diminished strength and sensation in the legs. A comparison of strength in the two first toes may reveal subtle early losses. You can determine this by putting your thumbs against the patient's two first toes in simultaneous dorsiflexion (L5) and

then plantarflexion (S1) against resistance.

Range of motion studies of the back help show its involvement. In addition to routine AP and lateral x-ray views, useful views of the back include standing lateral views and those in flexion and extension to detect the degrees of subluxation, and oblique views to detect possible isthmus fractures and the extent of apophyseal osteoarthritis.

The acute phase

All these studies should help plan a program of care aimed at diminishing the patient's immobility and the spasm that may accompany it. Resting the back helps ease the pain, but it may also intensify spasm. If the pain or spasm is intense, or if the radicular spread is extensive, advise complete bed rest for 1 or

more days. Bathroom privileges are permitted.

The bed must be quite firm. If a firm mattress is not available, a bed board may be placed under the mattress, or the floor with a thick rug may be used.

Pelvic traction by machine (favored by some therapists) is of questionable value. Bed traction can promote bed rest.

The subacute phase

In the subacute phase of his illness, once the patient is convinced that he is not weakening his legs or losing sensation, or resuming the identical pain syndrome, he may resume daily activities with or without a corset. Instruct men not to lift or bend from the waist. Tell them to bend their knees while shaving. Ask women to wear their tightest girdle—as a reminder not to bend, and as a mild support.

Advise rest periods in bed or on the floor for the first few days or weeks if the pain increases during the day. This is a convenient time to add heat (by pad or by thermophore pad) and massage (by patient or spouse). The patient may also do flexion isometrics for the abdomen, quadriceps tightening, and leg lifts. These may be performed as "one-inch" exercises. While the patient is supine, he raises the legs and holds them 1 inch off the floor. In the same way, he can raise the back off the floor 1 inch and hold it there for several seconds. During the back exercise, the knees are bent and the feet are planted on the floor. The patient may place his hands on the abdomen to judge the intensity of the muscle tightness.

Other useful exercises may help stretch the spastic back extensors. These are best done in the supine position on the floor. The knees are brought up to the

chest and held tightly with the arms for several seconds.

The best thigh exercises (to promote strength in squatting to avoid the need for back flexion) are deep knee bends, done while keeping the back quite straight. If the patient's legs are weak, he can use the wall as a support. He goes down only a few inches, and holds the position for 5 or 6 seconds before raising up. It is most important to build up leg strength. Patients who cannot squat all the way down are advised to squat halfway and pick up objects from the floor with a pair of tongs (the ordinary household barbecue utensils, or special ones available in orthopedic supply houses). Prolonged isometrics are contraindicated in hypertensive patients, however.

Medical therapy

Medication includes an occasional muscle relaxant, particularly late in the day or for sleep at night. Some of the more useful relaxants are orphenadrine, chlorzoxazone, carisoprodol, and methocarbamol. Diazepam is particularly useful when superimposed anxiety complicates management. Propoxyphene plus aspirin provides analgesia. Codeine is rarely needed during this phase of therapy, after the patient is up and around.

Flare-ups of apophyseal osteoarthritis may require more potent and long-sustained anti-inflammatory medications. These include higher dosages of salicylates or indomethacin or the newer propionic acid derivatives. The edema of an impinged nerve root may also be treated in this way—though this is controversial at the moment.

Losing weight helps

These patients generally need to lose weight, because added

pounds aggravate the sore area and require the patient to wear a corset for a longer time. And, of course, bed rest and diminished general activities often promote weight gain.

The chronic mild phase

During the mild chronic phase, exercises can be increased. Back isometrics may be added (although these are probably the least important muscles to exercise). Protection against excess motion need not be so stringent unless pain returns.

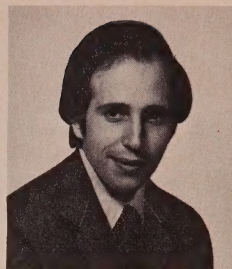
A good beginning exercise: The patient may try lifting with the back held straight. If he has built up enough leg strength to enable him to do such maneuvers correctly, he may lift weights of 10 or 15 pounds. To gauge his development of leg strength, watch while he picks up objects off the floor.

Flare-ups

Treat flare-ups as you did the initial or the subacute phase of the illness. Remind the patient to report any weakness or sensory loss.

Taper or withdraw the use of the lumbar corset when the initially small range-of-useful back motion has been increased. A corset potentially stiffens or weakens the back by excessive use. Nevertheless, it should be worn during periods of housework or job activities and discontinued during the least busy hours.

Some patients, including those with significant subluxation from spondylolysis, need to wear a corset for a long time. The type of garment is not nearly so important as the degree of firmness it provides. It must be tight enough to prevent those motions that aggravate the pain by promoting subluxation. These in-



Dr. Waxman is assistant professor of medicine at Louisiana State University School of Medicine. He serves on the staff at the Oschner Clinic in New Orleans. Dr. Waxman is certified by the American Board of Internal Medicine with a subspecialty in rheumatology.

clude excess flexion, flexion with twist, and progressive lordosis with prolonged standing. Sometimes, the corset stays need to be rebent or shortened to avoid pinching the patient while he walks or sits.

The pain-free interval

The pain-free interval is a difficult time, because the patient is anxious to resume his daily life. He may be able to—providing he has achieved a vigorous musculature and a lower weight, and providing he does not show pronounced disk narrowing or apophyseal osteoarthritis.

Advise him to increase his flexion and light lifting gradually. Caution him about avoiding sudden, heavy, unusual stresses in flexion. Warn him about twisting the lower back. You may want to add the entire series of Williams' back flexion exercises at this point. These exercises are well known to any physical therapist.

To prevent future flare-ups, talk to the patient and help him recognize the twinges of pain that may mean trouble. Remind him that the best way to care for his back is to avoid the activities and postures that hurt it. 

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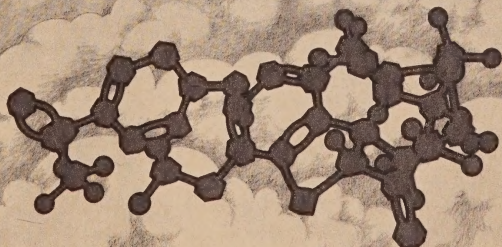
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Please see facing page for Brief Summary of prescribing information.

Cold hands and feet

Sir:

A healthy 20-year-old woman complains of cold hands and feet, with little apparent relationship to the air temperature or to time of day or specific activities. Her thyroid function studies are unrevealing, and there is no obvious evidence of vascular deficit. Do you have any suggestions to elucidate this problem?

—Jonas S. Rosenberg, M.D.
Denver

The lack of relationship to the air temperature probably eliminates simple (and usually benign) Raynaud's disease as a cause. Involvement of all four limbs points away from disease of the major arteries. Hormonal causes other than hypothyroidism (such as adrenal cortical deficiency), pharmacologic causes (such as tobacco, ergot, or methysergide), reflex constriction from rheumatoid arthritis, and central nervous system disorders (such as multiple sclerosis) must all be suspected. Polycythemia or macroglobulinemia would be rare in a 20-year-old woman, but should also be ruled out.

The most likely diagnosis in a woman this age is scleroderma. It may be impossible to confirm the diagnosis at this time, but

early clues may be found in the sedimentation rate or the hemogram. In some instances, x-ray studies of the esophagus will show areas of diminished activity and of dilation, even in the absence of dysphagia. Any suspicious areas of dermatitis should be biopsied.

If scleroderma is suspected but unconfirmed, I would not tell the woman. I would tell her to wear warm clothing, forbid smoking, and offer a supportive attitude, possibly along with an anxiety reducing drug.

—Edward A. Edwards, M.D.
Harvard Medical School

ANY QUESTIONS?



As a service to readers, CONSULTANT's authors will try to answer any questions pertaining to their topics.

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INDICATIONS: Indicated for the treatment of pyelonephritis, pyelitis, and cystitis due to susceptible *E. coli*, enterococci, *S. aureus* (it is not indicated for the treatment of associated renal cortical or perinephric abscesses) and certain strains of *Klebsiella-Aerobacter*, *Proteus* and *Pseudomonas*.

CONTRAINDICATIONS: Anuria, oliguria, or significant impairment of renal function; infants under one month; pregnant patients at term; known hypersensitivity.

WARNINGS: May cause hemolytic anemia of the primaquine sensitivity type, apparently linked to a glucose-6-phosphate dehydrogenase deficiency. (Such patients should be closely observed while receiving nitrofurantoin.) Discontinue the drug at any sign of hemolysis. Hemolysis ceases on withdrawal. Superinfections (limited to the genitourinary tract) may occur, most commonly due to *Pseudomonas*. Safety not established during pregnancy and lactation; should not be used in women of childbearing potential unless the expected benefits outweigh the possible hazards.

PRECAUTIONS: Peripheral neuropathy may occur. A fatality has been reported. Predisposing conditions such as renal impairment, anemia, diabetes, electrolyte imbalance, vitamin B deficiency, and debilitating disease may enhance such occurrence.

ADVERSE REACTIONS: Gastrointestinal Reactions—Anorexia, nausea, emesis are the most frequent reactions; less frequently, abdominal pain and diarrhea; rarely, hepatitis. This dose-related toxicity reaction can be minimized by reduction of dosage, especially in the female patient.

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Hematologic Reactions—Hemolytic anemia, granulocytopenia, leukopenia, eosinophilia, and megaloblastic anemia. Return of the blood picture to normal has followed cessation of therapy.

Neurological Reactions—Peripheral neuropathy, headache, dizziness, nystagmus, and drowsiness.

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SUPPLIED: Macrocrystalline (nitrofurantoin macrocrystals) is available in opaque, yellow capsules of 100 mg (coded "Eaton 009") and in opaque, yellow and white capsules of 50 mg (coded "Eaton 008") in bottles of 30, 100, 500, and 1,000 capsules; and in opaque, white capsules of 25 mg (coded "Eaton 007") in bottles of 100 capsules. Macrocrystalline Capsules, 50 mg and 100 mg, are also available in hospital unit-dose packages, strip-packaged in boxes of 100.



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for relief of stuffiness, drip and congestion*

INDICATIONS

Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the following indications as lacking substantial evidence of effectiveness as a fixed combination: Dimetapp Extentabs are indicated for symptomatic relief of allergic manifestations of upper respiratory illnesses, such as the common cold, seasonal allergies, sinusitis, rhinitis, conjunctivitis and otitis. In these cases it quickly reduces inflammatory edema, nasal congestion and excessive upper respiratory secretions, thereby affording relief from nasal stuffiness and postnasal drip.

CONTRAINDICATIONS: Hypersensitivity to antihistamines of the same chemical class. Dimetapp Extentabs are contraindicated during pregnancy and in children under 12 years of age. Because of its drying and thickening effect on the lower respiratory secretions, Dimetapp is not recommended in the treatment of bronchial asthma. Also, Dimetapp Extentabs are contraindicated in concurrent MAO inhibitor therapy.

WARNINGS: *Use in children:* In infants and children particularly, antihistamines in overdosage may produce convulsions and death.

PRECAUTIONS: Administer with care to patients with cardiac or peripheral vascular diseases or hypertension. Until the patient's response has been determined, he should be cautioned against engaging in operations requiring alertness such as driving an automobile, operating machinery, etc.

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Here is your chance to discuss important clinical questions with the experts. Send your questions to **CONSULTANT**. All of them will be referred to specialists for answers, and those of the greatest general interest will be discussed on these pages.



When arms are numb and tingling

Numbness, tingling, and heaviness in one or both arms, with preliminary findings normal—what does it mean, and what should you do?

Question by Richard H. Benedix, M.D. of Garden Grove, Calif.

Discussed by Robert Raskind, M.D., director of neurosurgery at Kern Medical Center, Bakersfield, Calif., **Adrian E. Flatt, M.D.**, director of the division of hand surgery at the University of Iowa, and **Albert B. Ferguson, Jr., M.D.**, professor of orthopedic surgery at the University of Pittsburgh.

Sir:

One of the most frustrating problems I see is the patient who complains of either gradual or

sudden numbness and tingling of either or both arms, usually with an associated heaviness.

I usually find no motor loss, no change in pain sensation, no associated pain, and normal tendon reflexes, arterial pulses, and color. *Can you comment on the possible causes?*

—**Richard H. Benedix, M.D.**
Garden Grove, Calif.

Sudden onset of numbness in the absence of objective neurologic changes is certainly not unusual, and can indeed be a frustrating problem. It may result from a scalenus anticus syndrome or thoracic outlet syndrome. Elevation of the arm and turning the head toward it against forceful

resistance may bring on a diminution or absence of pulse volume. This test should be done on both sides. In certain instances, positioning the arms in various postures produces reduction in circulation. Sometimes, merely elevating the hands above the head level produces blanching. Any of these alterations in circulation, arterial or venous, would suggest either the scalenus anticus syndrome or the thoracic outlet syndrome. Confirmatory evidence may then be obtained by a brachial angiogram or a venogram or both. If compression of vascular structures is so demonstrated, then a decompressive procedure—either a first rib resection or a sca-



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*See Adverse Reactions section in Brief Summary

Brief Summary

***Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).

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lenus anticus section—is indicated.

In most cases, however, no such objective evidence is found, and these complaints are usually functional. Hyperventilation may precipitate attacks.

In its early stages, a centrally located spinal cord tumor produces bizarre sensory alterations, but within several months, objective neurologic changes should accompany the symptoms.

—Robert Raskind, M.D.
Bakersfield, Calif.

I do not know a single most likely cause of this problem, but inadequate support of the shoulder girdle is often involved, particularly in middle-aged people and in women. In Europe, where women often carry heavy shopping baskets, complaints associated with drooping shoulder girdles are common. This is a straightforward mechanical problem, and patients usually respond readily to physiotherapy exercises directed to strengthening the shoulder girdles.

I am sure you have also considered neurologic disorders associated with degenerative changes in the cervical vertebrae in their lower region. Certainly this is the most common cause for the feeling of heaviness of the arm. Also, the old classic compression syndromes of either median or ulnar nerve around the wrist do produce the signs and symptoms you have described. Many patients are skeptical about this diagnosis; they find it hard to understand how the cause of pain that moves proximally can be at the wrist.

The problem in these cases, of course, is how far to carry the diagnostic investigation. I begin by trying physical therapy and I

may or may not do conduction studies for sensory and motor times in the ulnar and median nerves across the wrist and possibly the ulnar at the elbow. This is usually the full extent of my initial investigation. If the patient does not improve at all, I consider a consultation with a vascular surgeon.

—Adrian E. Flatt, M.D.
University of Iowa

Carpal tunnel syndrome is by far the most common cause of this type of complaint. This is readily diagnosed when the patient has atrophy, muscle weakness, and complete loss of sensation, but difficult to diagnose when the involvement has not progressed to this extent.

Typically, symptoms of carpal tunnel syndrome worsen with activity. The symptoms are absent in the morning, but after a day of using the wrist repetitiously, the patient complains of numbness and tingling. He is often awakened by this complaint at night, and gets relief by shaking the hand. Making a fist may accentuate the symptoms, as may bringing the hand into flexion.

When atrophy is not evident, subtle changes of denervation may be elicited by electromyography. There may be local tenderness over the median nerve at the point where the transverse carpal ligament crosses it. There will be no change in the vascular pattern.

The same symptoms can also arise from root compression in the cervical spine, associated with encroachment on the exit of the root, particularly from the level of C3 down to C6. The hand is typically involved with either C6 or C7 encroachment.

—Albert B. Ferguson, Jr., M.D.
University of Pittsburgh

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Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdose; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage. Use with care in patients with acute ulcerative colitis and discontinue use if abdominal distention or other symptoms develop.

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Dosage and administration: Lomotil is contraindicated in children less than 2 years old. Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) i.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) i.i.d. or two tablets (5 mg.) q.i.d. or two regular teaspoonsfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

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653

MEDICAL PROGRESS

FORENSIC STOMATOLOGY (First of Three Parts)

REIDAR F. SOGNAES, D.M.D., PH.D.

FORENSIC evaluation of oral conditions has shown that dentists can help the medical and legal professions solve problems of identification and serve the interest of justice, both in civil and in criminal litigations. To illustrate recent developments related to forensic odontology, I am aware of two new forensic handbooks,^{1,2} three student textbooks,³⁻⁵ one forensic-stomatology textbook (in Russian)⁶ and an international bibliographic listing,⁷ enumerating subject titles from various branches of the forensic sciences, including odontology. Within the space limitations of this Medical Progress series, the present review will deal with representative references to reasonably available journal articles originating from various parts of the world since 1970.

RECORDING METHODS FOR IDENTIFICATION

Studies on the surface configurations of the vermilion border of the human lips (*cheiloscopy*) and of the keratinized squamous-cell epithelium of the palate (*rugoscopy*) have revealed individual patterns partially explored for purposes of identification. A variety of other oral, dental and epidermal identifying features have been scrutinized for quantitative ante-mortem, post-mortem and bite-mark comparisons, ranging from routine radiology to scanning electron microscopy.

Cheiloscopy

Systematic evaluation of lip-print patterns has been primarily explored by Renaud⁸ and by Suzuki and Tsuchihashi.⁹ Labial wrinkles and grooves (*sulci labiorum*) could be subdivided into eight types, according to the Japanese investigators. The groove prints (*figura linearum labiorum rubrorum*) were initially classified on the basis of an examination of 280 Japanese of both sexes, six to 57 years of age, and of 18 pairs of uniovular twins between 12 and 13 years of age. Except for the twins, whose lip prints were similar, no lip prints manifested the same pattern in different persons. Apparently, the basic lip prints are genotypic, unchanged from before birth on.⁸

According to the Japanese analysis, the four most characteristic lip-groove patterns are vertical, branched, intersected and reticular. With some modifications one or more of these patterns can occur to the right and left of the midline of the lips, but with-

out necessarily being bilaterally symmetrical. Characteristic lip prints may thus be recorded in a cross-line diagram depicting the pattern within each of the four lip quadrants, resembling a conventional chart on dental status within each of the four jaw quadrants.

Subsequent Japanese investigations¹⁰ were extended to 1364 subjects of about equal sex distribution, three to 60 years of age, and a total of 49 teen-age uniovular twins. Repeated lip prints taken from one and the same person over a three-year period showed persistently consistent individual patterns. Such new lip-print studies can potentially contribute to personal and criminal identification, and possibly also to determination of parenthood relations and to supplementary explorations of human genetics. The vermilion border is peculiarly human — with or without lipstick. Indeed, a few criminal cases have been reported in which colorful lipstick imprints on some female underwear, on a pornographic magazine illustration and on a compromising envelope resulted in the elimination of one suspect and in the identification of another, who turned out to be a near relative.¹¹

Rugoscopy

The surface pattern of the palatal grooves and ridges known as rugae (i.e., rugoscopy) has not been widely used in identification. Comoy,¹² after reviewing the palatal anatomy, has indicated the means by which the palatal rugae may be examined and compared by combining photographs, impressions and models. Using plaster casts of the palate, he found that among a group of 200 persons there was slightly better rugae development in men than in women. But for each group the pattern was highly individual. Furthermore, the features appeared to be established early in life, and even reappeared, much like fingerprints, after traumatic or surgical removal. Relative dimension, morphology and number of the rugae are the criteria that have proved useful for classification.

The palatal mucosa is somewhat protected by the lips, cheeks and tongue, and preserved better than fingerprints after fire and other types of mass disasters. Hence, it has been suggested that the dentist take steps to include registrations of the palatal morphology for comparative identification purposes. Haines¹³ reported on a British airplane accident in which a number of the 78 victims wore complete dentures. Here, the palatal relief designs of the dentures, exhibiting the mirror image of the rugae pattern, were helpful in identification, as has also been reported from other countries.^{14,15}

For palatal-rugae comparison in forensic odontology

From the School of Dentistry and the Department of Anatomy, Center for the Health Sciences, University of California, Los Angeles (address reprint requests to Dr. Sognaes at UCLA School of Dentistry, Los Angeles, CA 90024).

gy, a Canadian study by Kogon and Ling¹⁶ has described a photographic superimposition technic that can be easily adapted to conventional photographic equipment. Also, it has been suggested that before proteolysis sets in, impressions be made of palatal rugae of unknown bodies as a potential adjunct to later identification by rugoscopy — e.g., for comparison with casts or prosthetic appliances that may be in the possession of the victim's dentist or family.

Radiology

Information obtained by x-ray photography of jaws and teeth can serve as one of the most objective types of information for evaluation of clinical treatment data, as well as for comparison between ante-mortem and post-mortem conditions. This kind of finding can lead to definitive evidence in a malpractice litigation and in cases of identification, and can also serve as convincing proof for exclusion of an individual. The latter situation was well illustrated during the Symbionese Liberation Army shoot-out in Los Angeles on May 17, 1974. Post-mortem x-ray examination of the jaws of the six persons, whose charred bodies were found in the rubble of the shoot-out, did not fit recent dental x-ray films taken in the case of Patricia Hearst. But roentgenology played an important part, together with other good ante-mortem dental charts, in the definitive identification of the victims, as reported by Vale et al.¹⁷

Technical details involved in post-mortem radiologic examinations have been discussed by various authors. There are also numerous other cases of individual homicide identifications as well as mass disasters that have emphasized the importance of radiological evidence. Precise superimposition of ante-mortem radiographs showing details of the crown and bridge work and the presence of root fillings and different degrees of healing of extraction sockets have proved particularly useful. Even minute fragments that may be present from burned victims can turn out to be helpful and should be saved for radiologic examination.

The most precisely oriented dental radiographs can be obtained after the jaws are separated and placed in appropriate position over the dental films. There are other methods, however, that can be applied at the post-mortem stage. For example, two recent reports^{18,19} have shown how one may use radioactive iodine (¹²⁵I) as a mobile radiation source for film exposure in mass disasters. Using such a small, portable intraoral radioisotope source with the film wrapped around the victim's face could be a quick supplementary aid to dental identification.

Another method that is used clinically is based on a panoramic type of x-ray, in which a synchronized radiation source is rotated opposite the film level around the head, so as to produce an ear-to-ear picture of both the jaws and the dentition. This method, however, would be somewhat difficult to use in a mass disaster because of the complexity of the apparatus and

the positioning of the head without any active co-operation on the part of the subject.

Holography and Stereomicroscopy

Application of holography to forensic dentistry has been suggested in a study by Altschuler²⁰ at the United States Air Force School of Aerospace Medicine, Brooks Air Force Base, Texas, on the basis of a combination of existing laser holographic and computer technology for intraoral use. Individual tooth prints can thereby be stored in computer data files, later to be retrieved for identification purposes as well as for other kinds of data treatment, involving oral diagnosis generally.

In a Swedish study, Frykholm et al.²¹ developed a dental measurement technic involving stereometric graphs. After preparing replicas and appropriate dental models, they made detailed contour-map comparisons. With a photogrammetrical type of stereomicroscope instrument (Autograph A 7, Wild), a three dimensional view could be obtained of the elevations and grooves present in the objects being examined. The first tests using this method included some 5000 measurements of dental students' dentitions and their experimental bite marks, comparing normal and irregular dental arches, respectively.²¹ Subsequently, the Swedish group applied the same method to criminologic investigation, demonstrating concordance between teeth and tooth marks.²²

Scanning Electron Microscopy

Thin, transparent replicas of surface structures played an important part during the early days of *transmission* electron microscopy in the late forties. Then, in the late sixties, soon after the introduction of *scanning* electron microscopy, several solid, nontransparent materials became suitable for precise surface exploration. During the period covered by this review, I have reported on a series of scanning electron-microscopy replica applications to anatomy, pathology and forensic science.²³⁻²⁸

The three-dimensional quality of scanning electron micrographs could now be explored by surface replication of both hard tissues²³ and soft tissues.²⁴ With this nondestructive, indirect approach, involving newer elastomeric dental-impression materials (e.g., silicones, polysulfides and polyethers), such replicas could be studied directly and could also be converted to positive epoxy molds and, in either case, could be shadow-cast with evaporated heavy metal in vacuum to make the negative and positive replicas conductive under the electron beam. This new approach proved useful in studies of dental wear marks caused by attrition and aging, as well as in observations on various bite marks vis-à-vis incisal tooth patterns. Applications to the latter types of cases have involved sex crimes and accidental and experimental bites, as well as the battered-child syndrome, examples of each to be dealt with in a subsequent section.

Meanwhile, from a technical and legal point of

view, it should be emphasized here that one is dealing with a relatively novel approach to forensic science. Thus, it is only a few years since I introduced this scanning electron-microscopy replica method as evidence in court.²⁵ That was in connection with a 1974 California sex strangulation murder involving scanning electron-microscopy examination of deep epidermal bite marks. Yet it is important to note that although new to the court, the technic was not new to science. Hence, it could be concluded that the contribution to the solution of that particular case by this method, though novel, was well within the rationale and capability of such a technic.^{25,26}

Beyond the above applications, I have also found that replications with these newer elastomeric dental-impression compounds offer promise of additional scanning electron-microscopy approaches to forensic science, including other types of epidermal replications (e.g., fingerprints²⁷), as well as ballistics.²⁸

Prosthetic Markers

Reports from a number of countries during the recent past have suggested that a universally understood system for identification of prosthetic dental appliances, especially full dentures, be developed. The British forensic odontologist, Haines,²⁹ on the basis of 18 literature references, evaluated eight air disasters involving 380 victims, of whom 50 had complete and 47 had partial dentures. But only seven of the dentures were marked with the victim's name.

If appropriately marked, dentures can present information about the patient's dental-treatment source. The artificial teeth may also have small markings to reveal their origin (i.e., the manufacturer of the teeth and hence, possibly, the country of the victim). In addition, the palatal morphology may ensure the connection of an isolated denture to a dismembered body, either by overall fit or by the pattern of the rugae — i.e., through rugoscopy, discussed above.

National preferences. Up to this point, it seems that different nations have relied on a variety of locally proposed identification markers. For example, Jerman,³⁰ an American investigator, has suggested the use of a strip of stainless steel identified as "shim stock" of a thickness of 0.026 mm. This metal has a very high melting point of about 1500°C; yet it is soft enough so that the identification number can easily be imprinted on the metal strip with an electric typewriter. The proposed system recommends the use of the patient's individual Social Security number as an identifying mark, as would be widely applicable to United States citizens. After the identifying strip is placed in the palate of the denture, it is covered with clear acrylic so as to be readily visible. As an additional advantage, it is suggested that the use of such a radiopaque metal label would make it readily identifiable if the patient should happen to swallow a denture so marked.

It is considered inadvisable to use a labeling system that involves elevated letters or numbers cast onto the carrying base of the dentures. In at least one

case Cavalier³¹ has warned that early neoplastic oral changes might have been attributed in part to chronic irritation of the mucous membrane from such elevated denture markers.

Some colleagues favor the simplest methods (e.g., identification data typed on material as inexpensive as tissue paper or foil), and a Danish colleague, Vestermark,³² has presented a concise ABC for the technical preparation and insertion of such information labels.

International coding systems. Toothlessness is international. Within the borders of the United States the importance of prosthetic markers is well illustrated by the fact that there are over 20 million edentulous Americans, whose identification cannot be made by characteristics of natural teeth. In Denmark all inhabitants, toothless or not, are registered with a 10-figure coding number in the central population register, which identifies the person's date of birth, sex, et cetera; similar registration data have been developing in West Germany, Holland, Belgium, France, Norway and Sweden.³²

After summarizing the variety of identification possibilities applicable to dental structures and associated restorations, a Canadian study by Dorion³³ has stressed the international need for appropriate marking of dentures, citing Sweden as one of the first countries to require this through its national dental laboratories. This uniform denture marking, it is believed, will achieve several purposes — namely, to prevent the loss of dentures, to help identify patients suffering from amnesia and to solve cases of homicide, suicide and mass disasters requiring post-mortem identification in the absence of fingerprints. Perhaps even a bank teller might accept a denture identification!

Would such marking of dentures impinge on the rights of the individual? The experienced British forensic observer, the late Dr. Warren Harvey, in making a plea for international adoption of prosthetic markers, added this observation back in 1971: "It is fascinating that Sweden, to whom many attribute quite liberal views, should have taken more than three years ago the seemingly totalitarian step of making the marking of dentures compulsory."³⁴

Radiopaque denture-base material. Going a step beyond purely forensic purposes, Harvey³⁵ also suggested that a radiopaque denture-base material, not merely the label, be used for an additional purpose — i.e., to ascertain if a person might have inhaled or ingested a denture. For he had ascertained that there were 13 cases of such denture accidents in 63 English hospitals during 15 years in a region with a population of about 3 million. Similarly, nine cases were observed in the Royal Air Force during a period of three years, and 21 cases of inhaled or ingested dentures in 55 hospitals in Scotland in one year only.

Miniaturized tooth markers. The most recent addition to dental marking systems has evolved from space-age technology. Thus, Samis³⁶ has proposed a so-called "Personal Dental Identifier," composed of alumina

substrate (i.e., a ceramic chip, 1.0 by 1.0 by 0.5 mm), carrying intelligence recorded in a microminiature mold, smaller than a pinhead, with name, Social Security number, etc. The microscopic "tombstone" can be made so minute that it may be hidden at the bottom corner of a small dental cavity, next to a so-called "Radiographic Disclosure Pin," placed so as to be readily visible for prompt identification in subsequent dental radiographs. In other words, even if only that single coded tooth were to be recovered from the site of a disaster, this buried information could lead to prompt positive identification, satisfactory to both the personal and the legal parties involved.

Dental Charting System

No dental charting method has received greater attention during the last few years than the so-called FDI two-digit system, summarized by Keiser-Neilsen³⁷ as adopted by the world congress of the Fédération Dentaire Internationale held in Paris in 1970. The first digits of the system designate, in clockwise sequence (beginning with the individual's upper right teeth), the four jaw quadrants of the permanent (one to four) and deciduous (five to eight) dentition, respectively. The second digits indicate the individual tooth in each of the four quadrants, one through eight for incisors to molars of the permanent teeth, and one through five for incisors to molars of the deciduous teeth (Table 1). The two-digit system has been better received by the academic community than by dental practitioners. Everyone must agree, however, that there is a great need for some forensic standardization. Mass disasters with modern intercontinental airlines tend to involve international passenger lists, and there have already been examples of considerable difficulties in trying to translate dental records from different countries.

Table 1. The New FDI Two-Digit Dental-Identification Symbols.

	(Right)								(Left)							
	PERMANENT DENTITION															
Maxilla	18	17	16	15	14	13	12	11	21	22	23	24	25	26	27	28
Mandible	48	47	46	45	44	43	42	41	31	32	33	34	35	36	37	38
	DECIDUOUS DENTITION															
Maxilla	55	54	53	52	51				61	62	63	64	65			
Mandible	85	84	83	82	81				71	72	73	74	75			

Computerization and Mass Disasters

Hitherto, there have been limited efforts to involve computerization in dental identification. From many points of view this would seem to be a logical development in a field with so many information units involved as human dentition. In a Canadian study Kogon et al.³⁸ illustrated a record-card system suitable for computerized comparison between ante-mortem and post-mortem dental data — e.g., teeth absent, present, treated or replaced. Once the computer au-

tomatically compared these data, unmatched findings were eliminated, and concordant data made available for a printout. In other words, the computer is not necessarily used for identification per se, but to sort out tentative possibilities and thus to direct attention to records that are most likely to lead to positive identification.

General and forensic pathologists now recognize more and more the need for dental input in connection with the identification of mutilated and burned bodies resulting from airplane crashes, as stressed by Eckert,³⁹ and from fires and explosions, as dramatically illustrated by Waaler.⁴⁰ Many specific mass disasters could be cited from many parts of the world in which dental findings proved of considerable importance and provided useful lessons. On the other hand, a recent editorial by Haines⁴¹ expressed concern regarding the lack of dental input after the gravest air accident in history, when 340 persons succumbed in a DC-10 crash near Paris in 1974. For it seems that dental services were offered in vain, despite the fact that identification by other means seemed impossible in a majority of the casualties.

Experience has demonstrated, according to a report by Van Wyck et al.,⁴² that the greater the degree of mutilation, the greater the importance of dental data. Yet there have been cases in which present-day dental restorations did not necessarily contribute to the identification. For example, Ashley⁴³ notes that at a British airport, the crash of an airplane carrying passengers from Asia involved the death of 47 Asiatic victims, among whom so few teeth had received the customary fillings that a total of only five restorations were found.

Another problem concerns the availability of dental records. For instance, in a 1970 Canadian airline crash, which caused the death of 109 passengers,⁴⁴ ante-mortem dental records could only be obtained for 67 of the victims, whereas no dental information of any kind was available for 42 of the dead. From 800 separate bags of human remains, 134 specimens of jaw and 37 denture fragments were received. After 16 days of hard work involving 12 dentists, dental identification was made in 72 per cent of the cases in which useful ante-mortem records were available. Being an international passenger list, this case also illustrated the diversity of systems used for ante-mortem records, which became another complicating factor. But of the 134 jaw specimens that were collected, 59 per cent could be identified by the dental team by comparison of the fragments with the available ante-mortem data.

Ashley et al.⁴⁵ have presented a helpful summary of the technics used by dentistry in connection with the identification of victims in aircraft accidents, indicating important contributions based, primarily, on experience of the dental branch of the Royal Air Force. In such disasters the availability of ante-mortem dental radiographs proved of most definitive value for post-mortem identification. According to a review by

Sopher,⁴⁶ summarizing statistics from American airplane fatalities, dental methods alone or in conjunction with other means could be shown to account for the identification of 36.7 per cent of 1000 victims in 21 aircraft accidents. In fact, in 30 per cent of the victims, the dentition alone resulted in positive identification. Thus, the need for formal organization of dental disaster teams as regular participants in such forensic investigations is sufficiently evident to become increasingly recognized at the international level.*

GENETIC MARKERS

In the past, the more familiar dental-record charts, radiographs and prosthetic restorations have served as the main dental evidence for identification purposes. But certain newer types of biologic and biochemical evaluations of oral tissues are now emerging that may provide supplementary information to the forensic investigator.

Sex Determination

An important initial step in identification of the dismembered remains of mass-disaster victims is the separation of sexes. Anthropologic skull measurements and the size of jaws and osseous protuberances for muscle attachments may give some clue to the sex of the victim. But it is only recently that sex and the single tooth have been associated by certain novel means of measurement at two levels of magnification. From a forensic point of view, the most important gross morphologic study in this connection is that by Anderson and Thompson at the University of Toronto.⁴⁷ These authors noted that the mandibular canine showed the greatest sex difference. Because of consistently larger dimensions in males than in females, it was found that the mandibular canine width alone permitted a 74 per cent correct sex classification. This could be a useful clue so far as this is one of the teeth least prone to dental disease during life and at the same time more likely to be recovered after death, even within fragmented jaw remnants at the scene of a mass disaster.

*The contributions of dentistry to the identification of persons who have died as a result of homicide, suicide, accident, military casualty or atrocity are far too numerous to be itemized in a review of this dimension. Many cases have employed some of the special forensic techniques described above, but the composition of the dental teams varies a good deal.

Dental know-how has been brought to the forefront of forensic identification and scientific advancements through three types of affiliations — namely, academic, military and law-enforcement agencies. In the United States forensic dentistry has largely been in the hands of dedicated dental practitioners on call to assist medical examiners, coroners and courts as needed in cases of local litigations, crimes or disasters. In many other countries the schools of dentistry have provided physical facilities and faculties for all practical, educational, scientific and organizational developments.

For example, under the leadership of Professor Gunnar Johanson, chief of forensic odontology at the Karolinska Institute, Sweden has now established a national mass-catastrophe team that includes three representatives of law enforcement, three of forensic medicine and three of forensic odontology. The last consist of the full-time academic members of the Odontological Faculties at the universities in Stockholm, Lund and Gottenburg. This team is on standby if, for example, an airplane crash were to involve Swedish nationals even outside their own border. No final identifications will be made by any investigator, whether he is a medical or an oral forensic pathologist.

Danish investigators, Jakobsen et al.,⁴⁸ have attempted to establish forensic sexing of incomplete maxillofacial and dental remains by histologic examination of the so-called neonatal line in ground sections from permanent first molars. In a test material these particular teeth, which normally begin to calcify at birth, show a higher prevalence of neonatal lines in females. In other words, the presence of this dental marker is considered important because the female, after completing fetal life, happens to be slightly ahead of the male in the development and location of this particular metabolic tooth marker, imprinted as a result of the physiologic impact at the time of birth.

By far the most interesting recent dental contribution to determination of sex stems from studies of sex chromosome fluorescence in microscopic tissue projections from single human teeth. Thus, Seno and Ishizu⁴⁹ have applied recent progress in chromosome-staining methods to separated cellular fragments from the dental-pulp structures, demonstrating the fluorescence of the chromatin, which originates from the distal portion of the long arm of the Y chromosome in the nucleus of male cells. They studied teeth from persons five to 77 years of age and found that the method was also applicable to pulp tissue from deciduous teeth and from teeth even after storage for various lengths of time.

Sex-determination tests by Ishizu et al.⁵⁰ have been attempted with oral specimens in addition to the pulp tissue. Thus, cellular material recovered from saliva consistently showed F-bodies in a high percentage of trapped male cells, but only in a very few cellular remnants harvested from female saliva. Even salivary residue on stamps and envelopes could be tested, and sex determined effectively, after periods of as long as six months of storage.

Blood Group and Isoenzyme Determination

Forensic dental research has explored the usefulness of blood-group tests on teeth, alveolar bone, oral epithelium and saliva. One of the first forensic applications of blood-group tests to teeth was in connection with identification of 30 persons killed in an accident in Poland, as reported by Mackerle and Loyka.⁵¹ The blood-group identity was found to be correct in over 80 per cent of some 40 samples examined. Forensic scientists in this field of dental research have been particularly active in Japan.⁵²⁻⁵⁴ Such work has improved on methodology by concentrating on an elution test, which has made it possible to perform tests on relatively small samples of jaws and teeth. For example, blood groups could be examined in the dental pulp and pulverized dental hard tissues on samples of less than 10 mg. Some tests have proved positive even after two years' exposure of the teeth to room temperature, to running water or to burial in sand to simulate post-mortem deterioration.

Similar elution technics have been used to demonstrate blood groups in alveolar bone for as long as two to seven years after death. In one case, the test gave a

lead that helped to establish identity of a skeleton 24 years after death. In 113 out of 115 alveolar bone specimens, Suzuki and Suzuki^{52,53} found that the blood type determined from the alveolar bone agreed with that from the blood of the same persons.

German workers have gone a step further in that Petersen and Heide⁵⁵ have demonstrated enzymatic genetic markers in dental-pulp tissues, in addition to studies of ABO blood-grouping identification by Schmechta and Lieske.⁵⁶ The isoenzyme systems of phosphoglucomutase (PGM), adenylate kinase (AK), adenosine desaminase (ADA) and 6-phosphogluconate dehydrogenase (6-PGD) could be revealed in dental-pulp tissue even after weeks of post-mortem decomposition.⁵⁵

Blood-group substances are also known to exist within the oral epithelium, as demonstrated within the stratum spinosum by two Scandinavian investigators. Thus, Dabelsteen and Fejerskov,⁵⁷ using a double-layer immunofluorescence technic applied to punch biopsies, found that the buccal mucosa had a much stronger expression of the blood-group antigen A than the palatal mucosa.

Of particular forensic importance is blood grouping of the secretory system, which is considered most easily tested in saliva. The amount of saliva deposited on subjects and objects related to a crime may often be relatively small. But around a bite mark there can be an area of about 15 cm² containing salivary remnants. At the same time, the ABO blood-grouping method is sensitive enough to give a positive reaction within a few fingerprints, from which the perspiration may also be chemically detectable in the neighborhood of the bite marks. For the testing of salivary deposits from a potential culprit, a cotton swab moistened with a little saline may serve as a sampling device. A report by Clift and Lamont⁵⁸ suggested that the saliva sample collection may be obtained by swabbing with a piece of damp cigarette paper held in a forceps to avoid contamination by hand contact.

Racial and Familial Dental Characteristics

Because international tourism may result in aviation mass disasters involving people from different nationalities and ethnic backgrounds, Haines⁵⁹ has reviewed racial characteristics pertinent to forensic dentistry. Perhaps the most distinct racial characteristic of individual teeth is the presence of shovel-shaped incisors. This feature has been reported in 95 per cent of American Indians, but can also occur in other races — for example, in 91 per cent of Chinese and nearly 50 per cent of Palestinian Arabs. Tall pulpal chambers (i.e., taurodontism), readily demonstrated in dental radiographs, are commonly found in South African and Australoid races. A bony exostosis of the palate is common in Eskimos and in a large percentage of Icelandic skulls; a similar exostosis of the mandible, torus mandibularis, has been observed in a third of the Aleutian population.⁵⁹

Aside from the very characteristic fully developed

shovel-shaped incisors, which are reasonably specific in the majority of mongoloid ethnic groups, it is as yet impossible to provide racial identification based on individual tooth morphologies within any one person. But Luntz⁶⁰ has suggested that computerized multivariate discriminant analysis might still become valuable if based on a combination of the most distinctive morphologic traits collected from systematic surveys of large population samples.

Supernumerary teeth and separation between teeth are characteristics of familial and hereditary background that can offer possible clues to identification. Furthermore, individuals with missing or peg-shaped maxillary incisors have been found to be definitely more common in groups of siblings of parents with this condition than in control families with a normal complement and alignment of the teeth. Thus, it has been suggested that a dominant autosomal gene is involved and that in some families the gene may have recessive or polygenic basis. Spacing between the teeth can be revealing, not only for post-mortem dental identification but also in terms of bite-mark evidence, as reviewed in a later section. Máchačová⁶¹ examined over a thousand subjects in their late teens from various parts of Slovakia for their incisor spacing or so-called medial diastemas. The condition was most frequent in the upper jaw. Specifically, in men and women alike, the maxillary central-incisor diastema was observed in about 3 per cent of the subjects, whereas diastemas between the mandibular central incisors were observed in about 1 per cent. In other words, when present and appropriately recorded, this condition appears rare enough to be of specific diagnostic value in identification.

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MASSACHUSETTS PHYSICIANS
ART SOCIETY

227. *Untitled*

(Exhibited at Annual Meeting of the
Massachusetts Medical Society, 1976)

Color Photograph

THOMAS S. ROY, II, M.D.

MEDICAL INTELLIGENCE



CURRENT CONCEPTS IN CARDIOLOGY

Determinants and Assessment of Cardiac Function

EUGENE BRAUNWALD, M.D.

DEFINITIONS

SEVERAL technics now available for the assessment of cardiac function will be discussed in these pages of the *Journal* during the next few months. The purpose of this article is to present relevant definitions and a framework for understanding these technics so that they can be applied to clinical problems in a rational manner.

At the outset, it is useful to consider the distinctions between *circulatory* function, *cardiac* function and *myocardial* function. The circulation consists not only of the heart but also of the blood vessels and the blood contained therein. Thus, circulatory failure may occur when the function of any one or combination of these elements is deranged. For instance, an impairment of *circulatory* performance may occur as a consequence of hypovolemia, at a time when *cardiac* and *myocardial* function may be entirely normal. The heart, in turn, consists not only of the contractile tissue — i.e., the myocardium — but also of the valves, coronary vessels, specialized automatic cells, conduction system, nerves and pericardium. Impaired *cardiac* function may result from a primary abnormality of the myocardium, as occurs in a cardiomyopathy or myocarditis, or from structural changes in the heart valves or pericardium that interfere with cardiac filling or emptying in the presence of normal myocardial function. In some patients cardiac failure is caused by a combination of myocardial and extramyocardial abnormalities. For example, in patients with chronic constrictive pericarditis, myocardial damage may result from infiltration of the heart muscle by pericardial inflammation and calcification. Extramyocardial abnormalities may also depress myocardial function. For example, in the presence of rheumatic valvular disease, the myocardium may become damaged by the long standing, excessive hemodynamic burden imposed by the valvular abnormality, and when this damage occurs, cardiac failure is both myocardial and extramyocardial. Arteriosclerotic heart disease, the

most common cause of cardiac failure, results from an extramyocardial disorder (coronary obstruction), which leads to ischemic impairment of myocardial function or myocardial necrosis (or both).

The heart's prime function is to deliver sufficient oxygenated blood to meet the metabolic requirements of the tissues, and heart failure is said to exist when the heart is unable to pump blood at a rate commensurate with these requirements. Accordingly, an accurate measure of the heart's ability to perform this task — i.e., determination of cardiac output — has been considered to be a key test of cardiac function. However, the cardiac output and the heart's contractile state cannot be related to one another in a simple manner since the contractile state is only one of several determinants of the heart's ability to eject blood. Therefore, measurement of the cardiac output alone is of limited value in characterizing the contractile state.¹ What, then, besides contractility, controls the volume of blood ejected by the heart? Since, at any given ventricular end-diastolic volume and heart rate, the cardiac output is a function of the extent of myocardial-fiber shortening, it is appropriate to identify the variables other than myocardial contractility that determine the extent of myocardial-fiber shortening.

MYOCARDIAL MECHANICS

It has been appreciated for a number of years that a fruitful approach to the understanding of cardiac function can be derived from study of isolated heart muscle. The geometric arrangement of cardiac muscle in situ, with its spiraling intertwining fiber bundles, complicates analysis of the behavior of individual myocardial cells. However, papillary muscles or trabeculae carneae, whose fibers run in a parallel fashion, have provided a suitable model. Study of the tissue in a myograph allows precise control of the physical and chemical environments, loading conditions and contraction frequency, and permits the elucidation of the effect on fiber shortening of varying these influences individually and in combination.

On the basis of studies of isolated cardiac tissue, it has been established that the extent of shortening is dependent on three distinct factors: the preload, which determines the heart muscle fiber's end-diastolic length; the afterload, which is closely related to the intramyocardial systolic tension; and the contractile or inotropic state of the myocardium.² At any level of the contractile state, the extent of shortening varies inversely with the afterload and, within limits, directly with the preload. When the afterload is progressively raised, an increasing proportion of the muscle's contractile activity is expended in the generation of tension, and a smaller fraction is expended in myocardial-fiber shortening.³ Only when preload and afterload are constant do the extent and velocity of myocardial-fiber shortening vary directly with the heart's contractile state. Obviously, the total extent of muscular shortening per minute also depends on the con-

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traction frequency, and in the intact heart, heart rate is the fourth major determinant of cardiac output.

Although the aforementioned complex geometric arrangement of myocardial fibers makes it more difficult to express the fundamental determinants of the extent of contraction *in vivo* in precise terms, it is evident that the three factors that affect the extent of shortening of isolated cardiac muscle also influence the stroke volume of the intact heart. For example, when aortic-outflow impedance is gradually raised while ventricular end-diastolic volume is held constant, stroke volume declines until a level of impedance is reached at which the maximum force-generating capacity of the myocardium is exceeded — i.e., at which the contraction becomes isovolumetric and ventricular ejection ceases. Conversely, left ventricular stroke volume rises when afterload is reduced, which may occur as a result of arteriolar dilatation, a reduction in blood viscosity, the opening of an arteriovenous fistula, the development of mitral regurgitation or the administration of a vasodilating agent. From these considerations it should be clear that when changes in afterload occur, there are reciprocal alterations in stroke volume, which need not reflect changes in the myocardial contractile state.

The effects of simple alterations of preload on cardiac output are more widely appreciated. Thus, the depression of cardiac output that occurs with hypovolemia, the displacement of blood from the thorax with positive-pressure ventilation or with cardiac compression, as in pericardial tamponade, may be explained solely on the basis of a reduction of preload, and the elevated cardiac output in some patients with polycythemia vera or acute glomerulonephritis need not reflect an augmented contractile state, but instead a higher preload resulting from hypervolemia.

For practical purposes it is useful to identify a change in contractile state as an alteration in function that is independent of variations in preload or afterload. When the adrenergic drive to the heart is minimal, or has been blocked with a beta-adrenergic receptor blocker, a basal level of contractility can be defined.

The level of activation appears to be influenced importantly by the quantity of calcium ion made available to the contractile apparatus and in contrast to skeletal muscle, heart muscle is not ordinarily fully activated during contraction. When the contractile state is augmented (i.e., when the level of activation is elevated by an intervention, such as an increase in contraction frequency or the addition of norepinephrine), the peak force developed, as well as the rate of force development rise and the time to reach peak force, declines. Inotropic interventions do not usually alter the relation between the length and tension of the resting muscle, but by definition they do change the actively developed tension at any given muscle length.

In studying the mechanics of cardiac contraction it

is helpful to analyze not only isometric contractions but the characteristics of the muscle during shortening as well. To accomplish this analysis, one end of the papillary muscle is attached to a lever system so that it is free to shorten, and both the extent and the velocity of shortening are measured. The maximum velocity of shortening depends on the load, and the relation between the tension (force) developed and the velocity of contraction is expressed by the force-velocity curve: the lower the load, the higher the velocity of shortening. Velocity of shortening with zero load, (i.e., the maximum velocity of unloaded shortening, termed V_{max}) is not normally measured directly, but extrapolation of the curve to zero load approximates this velocity. When the load is increased to the point at which no muscle shortening occurs, the isometric force developed at that muscle length is recorded.

When the initial muscle length — i.e., the preload — is altered, the force-velocity curve is shifted so that both the velocity of shortening with any given load and the isometric force are changed (Fig. 1). Notably, when the contractile state of the muscle is aug-

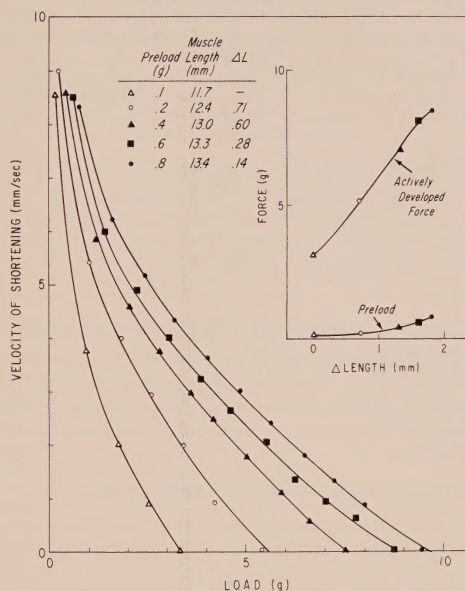


Figure 1. Relation between Peak Velocity of Afterloaded, Isotonic Shortening and Total Load at Several Initial Muscle Lengths in a Cat Papillary Muscle (Reproduced from Braunwald et al.² with the Permission of the Publisher).

The insert at the right shows the resting and developed active force at these various lengths. When initial muscle length is increased, the actively developed force is augmented, as is the velocity of shortening at any individual load. The maximum velocity of shortening with the preload alone is little altered. Moreover, if these curves were to be extrapolated back to zero load, this value would also show little if any change.

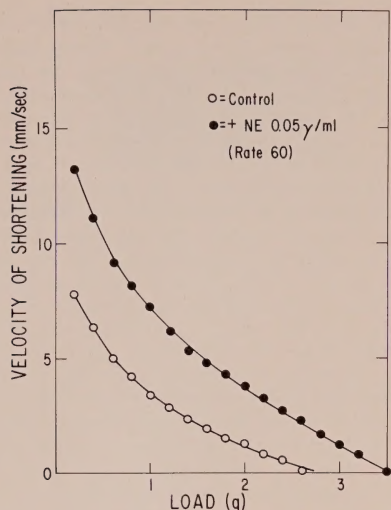


Figure 2. Effects of the Addition of Norepinephrine (NE) on the Force-Velocity Relation of the Cat Papillary Muscle (Reproduced from Braunwald et Al.² with the Permission of the Publisher).

Norepinephrine induces an increase in the velocity of shortening at any load, the maximum force of isometric contraction, and the maximum velocity of unloaded shortening.

mented, the rate of tension development, as well as the velocity and extent of shortening at a given load, is increased. Indeed, the entire force-velocity curve is shifted upward and to the right, with an increase in both isometric force and V_{max} (Fig. 2).

CLINICAL METHODS FOR ASSESSING CONTRACTILITY

The simplest clinical approaches to examining changes in the heart's contractile state are based on standard methods for measuring intravascular and intracardiac pressures, cardiac output and ventricular volume.

Intracardiac Pressures, Volume and Blood Flow

In the resting, conscious state at a normal heart rate and afterload, when the left ventricular end-diastolic volume is clearly elevated (i.e., >110 ml per square meter), and the stroke volume and cardiac index are within normal limits or reduced, cardiac contractility may be considered to be depressed. (Whenever valvular regurgitation is present, total stroke volume — i.e., the sum of forward and regurgitant flow — should be measured.) At any heart rate, when ventricular end-diastolic pressure and volume, as indexes of ventricular preload, and aortic pressure, as an index of afterload, are held constant, the stroke volume, stroke work, stroke power, peak left ventricular pressure rise (dP/dt) and ejection velocity vary as a direct function

of the contractile state of the myocardium. Simplified methods using pressure data alone have been employed to determine V_{max} during the brief isovolumetric phase of ejecting beats. In such derivations it has been held that if the contraction of the myocardium during isovolumetric contraction is truly isometric, pressure and tension are linearly related to one another, and wall stress need not be calculated to derive V_{max} . Also, to apply this method, it is necessary to estimate the elasticity of cardiac muscle. The validity of these assumptions and the accuracy of these estimations are open to some question.

Isovolumetric-Phase Indexes

In evaluating acute changes in contractile state, the isovolumetric phase indexes (e.g., maximum dP/dt and dP/dt at a developed pressure of 40 mm Hg) are useful. These indexes are relatively simple to obtain and are very responsive to acute changes in the contractile state, as well as insensitive to steady-state changes in afterload, and rise only slightly with large increases in preload.⁴ Therefore, they are of considerable value in determining whether a specific intervention, such as a drug, affects contractility. However, the range of normal values of the isometric-phase indexes is wide, and they are therefore of little value in determining whether or not the basal contractile state in any given person is normal.

Ejection-Phase Indexes

On the other hand, measures of the ejection phase of contraction, such as the mean and peak velocity of circumferential fiber-wall shortening (V_{CF}) corrected for end-diastolic circumference, the ejection fraction and the systolic ejection rate, appear to be useful for characterizing the basal contractile state. It has been shown in the presence of chronic pressure overloading that over long periods, wall stress (afterload) generally remains normal because of the development of compensatory ventricular hypertrophy. In laboratory animals subjected to chronic volume overloading, the preload, reflecting sarcomere length, does not change but remains maximal as the ventricle slowly dilates in response to this stress. Thus, to evaluate the basal contractile state in patients, even those with chronic changes in cardiac loading, ejection-phase indexes of contractility can be used, even though they are affected by acute changes in preload and afterload.⁵ However, because of their sensitivity to variations in afterload, these indexes are of less value in the detection of acute changes in contractility. As indicated above, the isovolumetric-phase indexes are more useful for this purpose.

In practice, V_{CF} is calculated from angiocardio-graphic or echocardiographic measurements; the difference between end-diastolic and end-systolic circumferences is expressed in circumferences per second. Whether or not the V_{CF} (mean or maximal) is

more sensitive than the ejection fraction or the mean systolic ejection rate is not clear at present. With mild impairment of contractility these variables may be depressed although cardiac output and intraventricular pressure are within normal limits. However, with further depression of left ventricular function, stroke volume and ultimately the cardiac index decline, whereas ventricular end-diastolic pressure and volume rise.

Stress Tests

A number of approaches have been used for detecting mild to moderate left ventricular dysfunction or impaired myocardial reserve. The potential value of subjecting the left ventricle to stress is emphasized by the fact that not infrequently the basal values for all the above-mentioned indexes are within the same range in patients with suspected depressions of cardiac function as they are in normal persons. The approaches that have been employed include measurement of the circulatory changes occurring during acute stresses, such as pedaling a bicycle ergometer, isometric handgrip or increased afterload. The determination of the effects of these stresses on either the isovolumetric-phase or the ejection-phase index may help detect abnormal myocardial reserve when no abnormality is apparent in the basal state.

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AMNIOTIC-FLUID CORTISOL AND HUMAN FETAL LUNG MATURATION

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RECENT studies suggest that cortisol plays an important part in fetal lung maturation. Lower cortisol levels were found in umbilical-cord blood of infants in whom the respiratory-distress syndrome de-

veloped than in normal infants of comparable gestational age,¹ suggesting a physiologic link between endogenous fetal cortisol production and maturation of the fetal lung. With a radiotransinassay specific for unconjugated cortisol it was shown that after an initial rise in amniotic-fluid cortisol around the 20th week of gestation, there is a plateau until at least 35 weeks, followed by a rapid rise, particularly in the two weeks before the onset of spontaneous labor.²

A pattern of rising levels in amniotic fluid after 35 weeks is also exhibited by the lecithin/sphingomyelin ratio,³ the palmitic acid concentration⁴ and the palmitic/stearic ratio,⁵ all of which reflect the increasing lecithin concentration of amniotic fluid. To date two groups have explored the relation between amniotic-fluid lecithin and cortisol. Sivakumaran et al.⁶ found the same trends through gestation in cortisol levels and lecithin/sphingomyelin ratio but a very weak correlation between individual cortisol and lecithin/sphingomyelin ratio in 114 amniotic-fluid samples. On the other hand, Fencel and Tulchinsky⁷ demonstrated a good correlation between the two measurements for 43 amniotic fluids.

The present study was designed to resolve this difference, and to evaluate the potential clinical usefulness of a rapid cortisol determination as an index of fetal lung maturation.

MATERIALS AND METHODS

Amniotic fluids were obtained at hysterotomy, at amniocentesis or at rupture of the membranes during spontaneous or induced labor. Fluids contaminated with blood or meconium were discarded, and the remaining 98 samples were frozen until analyzed.

The method used to measure the palmitic acid levels in amniotic fluid was based on those of Alcindor³ and Warren⁸ and their colleagues. The lipids were extracted as described by Hanson and Olley⁹ and hydrolyzed, after which the fatty acids were methylated and the fatty acid pattern analyzed and quantitated by gas-liquid chromatography (Hewlett-Packard model 583A gas chromatograph with automatic integrator). The precision of the methods was estimated by analysis of the same amniotic fluid with each group of samples run. Within-assay variation was ± 6.0 per cent for palmitic acid and ± 5.5 per cent for palmitic/stearic ratio, whereas between-assay variation was ± 13.8 per cent and ± 19.2 per cent respectively. Storage of the control amniotic fluid frozen for a period of two months had no effect on the measurements.

Unconjugated cortisol in 0.03 ml of amniotic fluid was assayed in duplicate by competitive binding to horse transcortin as outlined previously.¹⁰ Two techniques of sample preparation were used. One involved methylene chloride extraction before assay (preparation B of Murphy¹⁰ with a within-assay variation of ± 8.5 per cent, between-assay variation of ± 11.0 per cent and recovery of 91.4 ± 4.1 per cent [S.D.]). The other technic (preparation C of Murphy¹⁰) employed heating without extraction and was much quicker — results were obtained in as little as an hour. Recovery was complete, and variations within and between assays were reduced to ± 3.2 and ± 5.1 per cent respectively. A good linear correlation was found for 48 sets of values with the two methods (correlation coefficient, $r = 0.95$, $P < 0.001$). The values obtained with the shorter method were slightly higher ($+20$ per cent), probably owing to the presence of cortisol sulfate, which is not extracted in the longer method. Because of the close agreement between the two methods subsequent analyses employed the shorter method only. Freezing for as long as six months had no effect on the values obtained.

The associations between cortisol concentration and palmitic ac-

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id concentration and palmitic/stearic ratio were evaluated by simple regression analysis using Pearson's correlation coefficient r (corresponding to the analysis used by Sivakumaran et al.) and also by rank correlation with Spearman's correlation coefficient designated r_s (corresponding to that of Fencel and Tulchinsky).

RESULTS

Effect of Removing Sediment from Amniotic Fluid

Six samples were excluded from the original group. These were thick, white fluids in which cellular debris settled if they were left undisturbed for a few minutes. Whereas the palmitic acid concentrations were much lower if the debris settled out, even falling to levels indicative of lung "immaturity" (see below), in two cases of over 38 weeks' gestation, the palmitic/stearic ratio did not fall to such an extent and maintained mature values. Cortisol levels also fell after settling, indicating that cortisol is also present in the cellular debris.

Amniotic-Fluid Analysis

Measurement of palmitic acid concentration and palmitic/stearic ratio in all the samples from 10 to 43 weeks' gestation revealed low values persisting until 34 weeks, whereupon both began to rise (Fig. 1). This increase continued until term. When palmitic acid concentration and palmitic/stearic ratio were compared the correlation was good ($r = 0.82$, $P < 0.001$) and was improved slightly by comparison of log palmitic acid vs. palmitic/stearic ratio ($r = 0.89$, $P < 0.001$). The critical palmitic acid concentration needed to indicate fetal lung maturity (viz., $70 \mu\text{M}^*$) corresponded to a palmitic/stearic ratio of 2.6, values usually attained between 34 and 35 weeks' gestation. There were few clinical discrepancies between palmitic acid concentration and palmitic/stearic ratio.

Mean cortisol levels at each gestational age are also given in Figure 1. There is evidence of an increase during the second trimester, with little change up to 37 weeks, when a terminal rise occurred to a level above $20 \text{ ng per milliliter}$. The trend in cortisol levels differed from those of palmitic acid concentration and palmitic/stearic ratio in that there was an initial rise in cortisol at about 20 weeks (possibly influenced by the small sample size of two, both of which were Rh incompatible), and the terminal rise occurred later.

Although mean levels of palmitic acid concentration, palmitic/stearic ratio and cortisol all tended to increase during the latter part of gestation, the correlation of cortisol with palmitic acid concentration for the 92 amniotic fluids, considered individually, was weak ($r = 0.48$, $P < 0.001$); a slightly higher correlation was found between cortisol and palmitic/stearic ratio ($r = 0.65$, $P < 0.001$). If only the 54 samples obtained after 28 weeks' gestation (those of interest from the practical point of view) are included in the analysis, the correlation coefficients dropped to 0.28 ($P < 0.05$) and 0.55 ($P < 0.001$) respectively, indicating that the low values of all three measurements seen during early pregnancy serve to anchor the regression lines.

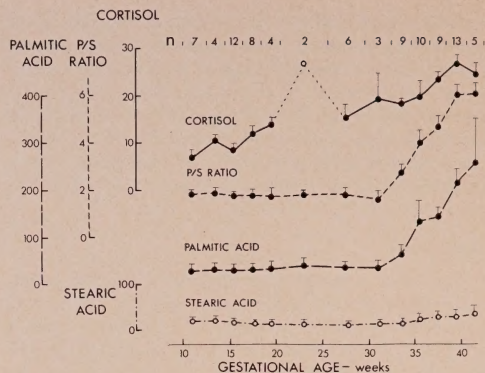


Figure 1. Mean Concentrations of Palmitic (in Micromoles per Liter) and Stearic Acid (in Micromoles per Liter), Palmitic/Stearic (P/S) Ratios and Cortisol Concentrations (in Nanograms per Milliliter) during Gestation (Standard Errors Are Indicated).

The association between the variables becomes more obvious (Table 1) when the "high-risk" amniotic fluids (i.e., those from patients with diabetes and severe Rh disease) are excluded from the analysis and the remaining results are classified according to high ($>20 \text{ ng per milliliter}$) vs. low ($<15 \text{ ng per milliliter}$) cortisol levels and mature vs. immature palmitic acid concentrations, in samples over 28 weeks. Five of six samples with low cortisol had immature palmitic acid concentrations, whereas 21 of 24 with high cortisol had mature palmitic acid concentrations. Similar results were seen for palmitic/stearic ratios. Despite a significant chi-square value ($P < 0.05$), almost a third of the samples with high palmitic acid concentrations and palmitic/stearic ratios had low cortisol. When the high-risk group was considered, five second-trimester amniotic fluids had high cortisol levels. Discordant results were also seen in one anencephalic infant born at 33 weeks' gestation — i.e., low palmitic acid concentration ($42 \mu\text{M}$) and high cortisol ($21 \text{ ng per milliliter}$). Three patients with delivery within 48 hours of

Table 1. Relation between Cortisol Levels, Palmitic Acid Levels (PA) and Palmitic/Stearic Ratios (P/S) in Amniotic Fluids from 43 Apparently Uncomplicated Pregnancies of over 28 Weeks' Duration.*

CORTISOL	PA <70 μM	P/S <2.5	PA 70-100 μM	P/S 2.5-3.5	PA >100 μM	P/S >3.5
ng/ml						
	no. of pregnancies					
15	5	5	0	0	1	1
15-20	3	3	1	2	8†	7†
20	3‡	1	1‡	4§	21¶	20

*PA vs cortisol: $r = 0.28$, $r_s = 0.50$; P/S vs cortisol: $r = 0.55$, $r_s = 0.55$.

†2 during labor; in 1 respiratory-distress syndrome developed after cesarean section.

‡1 during labor.

§3 during labor.

¶16 during labor; 3 by amniocentesis within 48 hr of delivery of normal infants.

||15 during labor; 3 by amniocentesis within 48 hr of delivery of normal infants.

amniocentesis had both high palmitic acid concentrations (and palmitic/stearic ratios) and cortisol levels, and in one of the infants the respiratory-distress syndrome developed. Of the two infants who did have the syndrome, one was delivered by cesarean section at 30 weeks' gestation because of a placenta praevia, and the palmitic acid concentration (45 μ M) and palmitic/stearic ratio (1.92) were low, as expected, but the cortisol was high (30.7 ng per milliliter). The second baby in whom the respiratory-distress syndrome developed was also delivered by cesarean section, but in this case the cortisol was low (16 ng per milliliter) and the palmitic acid concentrations (127 μ M) and palmitic/stearic ratio (5.1) were high although not unexpected for 39 weeks' gestation.

Table 2. Relation between Amniotic-Fluid Lecithin and Cortisol.

VARIABLE STUDIED	FENCL & TULCHINSKY ⁷	SIVAKUMARAN ET AL. ⁶	PRESENT STUDY
No. of samples	43	114	98
Sample type	Normal	High risk	Mixed
Cortisol method	"Total" cortisol by radioimmunoassay (mostly conjugated)	"Cortisol" by radioimmunoassay	Unconjugated cortisol (83%) by radiotrans-inassay
Mean cortisol (ng/ml)			
At 20 - 34 wk	32	139	10
At 35 - 40 wk	72	170	27
Lecithin estimation	L/S*	L/S	P:† P/S‡
Statistical analysis	Rank correlation (all ages)	Multiple regression (>28 wk)	Both
Correlation of cortisol vs lecithin	$r_s = 0.83$	$r = 0.37$	All ages: P: $r = 0.48$, P/S: $r = 0.65$ >28 wk: P: $r = 0.28$ $r_s = 0.50$ P/S: $r = 0.55$ $r_s = 0.55$

*Lecithin/sphingomyelin ratio.

†Palmitic acid concentration.

‡Palmitic/stearic ratio.

DISCUSSION

The correlations obtained in this study are intermediate between those of Fencl and Tulchinsky⁷ and Sivakumaran et al.⁶ (Table 2). It appears that although there is a positive relation between the two, the amniotic-fluid cortisol level cannot be used with confidence to predict lung maturation as indicated by lecithin production.

Methodologic differences may be important — the values for cortisol obtained by Sivakumaran et al. are much higher than those of Fencl and Tulchinsky although the latter recognized that they were also measuring conjugates. It is possible that conjugated cortisol is a better index than unconjugated cortisol.

The determination of palmitic acid concentration (or palmitic/stearic ratio) rather than lecithin/sphingomyelin ratio has several advantages. It provides a quantitative rather than a semiquantitative estima-

tion that can be quality-controlled since there is little alteration with time over several months. Palmitic acid concentration correlates very well ($r = 0.93$) with total amniotic-fluid lecithin.¹¹ As compared with methods for lecithin that depend on phosphate determination, the gas-liquid chromatography method takes less time.

The samples in this study were neither filtered nor centrifuged. Our observations of large differences in palmitic acid in thick samples when the supernatant was compared with the mixed sample are in keeping with those of Abramovitch et al.,¹² who found 79 per cent of lecithin in the precipitate of centrifuged fluid, and of Nelson,¹³ who found that filtering samples collected near term removed approximately 90 per cent of the lecithin. Since the lecithin-containing material from the lung is presumably cellular debris it may be preferable to include this material in the analysis.

Several biologic factors may also be responsible for this rather poor correlation. Cortisol is known, at least in the adult, to be secreted in a pulsatile manner and to have a circadian rhythm. Such fluctuations, if they occur in the fetus, might be reflected in the amniotic-fluid cortisol level. Another possibility is that amniotic-fluid cortisol is a poor indicator of the intrapulmonary level since fetal lung tissue is known to contain 11 β -dehydrogenase, which converts cortisol to cortisone.¹⁴ Fetal stress is another factor that may raise intra-amniotic-fluid cortisol levels; in a previous study we showed that three of four infants who died of Rh incompatibility shortly after amniocentesis before 30 weeks' gestation had levels of cortisol in excess of 20 ng per milliliter.² Our most recent findings suggest still another explanation: we have shown that the chorionic membrane converts the metabolite cortisone (biologically inactive in the fetus) to cortisol from about 17 weeks to term, thus providing an extra source of amniotic-fluid cortisol that may be independent of the blood level.¹⁵ Finally, factors other than cortisol, such as the thyroid hormones, may also play an important part in lung maturation.¹⁶

We are indebted to Dr. R.A. Kinch and the other members of the Department of Obstetrics and Gynecology for their co-operation.

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MACROGLOBULINEMIA AND HAIRY-CELL LEUKEMIA

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LEUKEMIC reticuloendotheliosis, or hairy-cell leukemia, is a distinct clinical entity characterized by the proliferation of cells that have prominent cytoplasmic projections and contain the tartrate-resistant isozyme 5 of acid phosphatase.¹⁻³ Although the clinical and morphologic features of this disease are widely known, there is considerable disagreement over whether the leukemic cell belongs to the lymphocyte or monocyte lineage.⁴ In the unusual case of hairy-cell leukemia reported below, the leukemic cells produced a monoclonal IgM, thereby substantiating the lymphocyte derivation of the neoplastic cells in this patient. The findings emphasize the wide clinical and biologic spectrum of B-cell neoplasms.

CASE HISTORY

In 1959 a 60-year-old, medically knowledgeable man (he had maintained careful records of his blood studies since 1955) noted an increase in the erythrocyte sedimentation rate to 31 from a previous mean of 11 mm per hour. Paper protein electrophoresis showed a small M component in the fast gamma region. In 1965 a physician noted splenomegaly. At that time the hemoglobin was 13.5 g per deciliter (a reduction from the previous mean of 15 g per deciliter). The white-cell count was 6822 per microliter, with 54 per cent neutrophils, 32 per cent lymphocytes, 2 per cent monocytes and 3 per cent eosinophils. Quantitative immunoglobulins by ultracentrifugation in 1966 showed a total 19S globulin of 800 mg per deciliter. Rouleau formation was noted on the peripheral smear, and

the erythrocyte sedimentation rate was 50 mm per hour. Bone-marrow aspiration showed a mild lymphocytosis (count of 25 per cent). In 1970, the hemoglobin was 13.3 g per deciliter, and the white-cell count 10,500 per microliter, with 57 per cent neutrophils, 37 per cent lymphocytes and 3 per cent monocytes. The patient remained asymptomatic throughout this period while adhering to a strict low fat diet and running approximately 11 km per day. In December, 1975, he noted extreme fatigue after running only 3 km. His exercise tolerance decreased rapidly until he had to give up running in January, 1976. At that time he also noted ankle edema. When seen by his physician, he was found to be anemic, with a hemoglobin of 7.5 g per deciliter and a white-cell count of 47,000 per microliter. He was referred to UCLA for additional diagnostic studies.

Physical examination revealed a pale, thin man in no acute distress. There was no appreciable lymphadenopathy, and the lung fields were clear to auscultation and percussion. A systolic ejection murmur was audible over the apex. The liver was not enlarged, but the edge of the spleen was palpable 10 cm below the left costal margin. The hemoglobin was 8.5 g per deciliter, and the white-cell count 66,000 per microliter, with 98 per cent lymphocytes and 2 per cent neutrophils. Approximately 20 per cent of the peripheral blood lymphoid cells showed fine, hairlike projections. The platelet count was 104,000 per microliter, and the reticulocyte count 6.8 per cent. A peripheral blood smear showed rouleau formation and prominent anisocytosis, with some teardrop cells. The Coombs test was negative, and routine blood chemical findings were unremarkable. Massive splenomegaly was confirmed on radioisotope scan, and the liver was demonstrated to be of normal size. The bone marrow was difficult to aspirate, but adequate material was obtained and showed almost complete replacement of the normal architecture by medium-sized to large-sized lymphoid cells. The total serum protein was 7.4 g per deciliter, with 22.5 per cent gamma globulin. Quantitative immunoglobulins were as follows: IgA, 100, IgG, 450, and IgM, 1025 mg per deciliter. Cellulose acetate electrophoresis disclosed a clear M component migrating between the beta and gamma globulins. Immunoelectrophoresis showed an atypical IgM precipitin arc.

The neoplastic cells stained prominently for acid phosphatase that was tartrate resistant. Polyacrylamide-gel electrophoresis confirmed that the acid phosphatase activity migrated almost completely as isozyme 5.² Transmission electron microscopy was consistent with the lymphoid nature of these cells, and scanning electron microscopy demonstrated prominent and numerous cytoplasmic projections. The peripheral blood lymphocytes revealed a minimal response to concanavalin A and phytohemagglutinin over a wide range of concentrations.

Ninety-two per cent of the peripheral blood lymphocytes stained positively for membrane-bound immunoglobulin. Ninety per cent formed rosettes with sheep red blood cells coated with IgM antibody and complement (EAC), and 51 per cent formed rosettes with trypsinized sheep red blood cells coated with IgG antibody (EA). Only 4 per cent of the peripheral blood lymphocytes were T cells as defined by spontaneous rosette formation with untreated sheep red blood cells.

With use of immunoglobulin class-specific fluorescent antisera, 90 per cent of the patients' peripheral blood lymphocytes were shown to carry surface IgM, and 78 per cent had surface IgD. After staining with both antisera simultaneously, the proportion of reactive cells was 88 per cent. The positive cells showed good cap formation with both anti-IgM and anti-IgD, whereas there was no staining with anti-IgA or anti-IgG.

Peripheral blood lymphocytes were fixed and then stained with the same specific fluorescent reagents to demonstrate cytoplasmic fluorescence, and 81 per cent showed cytoplasmic IgM. There was no cytoplasmic reactivity with anti-IgD, anti-IgA or anti-IgG.

Studies of immunoglobulin synthesis *in vitro* were performed with the patients' peripheral blood lymphocytes. The cells were suspended in culture medium devoid of leucine, and tritiated leucine was added. At intervals, the cells and supernatant medium were harvested, and the amount of radioactivity incorporated into immunoglobulin, and total protein was measured.³ Approximately 1 per cent of the total protein manufactured by the lymphocytes was immunoglobulin. The radioactive immunoglobulin was reduced, al-

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Supported by grants (CA 15688, CA 15619 and CA 12800) from the U.S. Public Health Service and by a grant from the California Institute for Cancer Research.

CARDIOVASCULAR BIRTH DEFECTS AND ANTENATAL EXPOSURE TO FEMALE SEX HORMONES

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Abstract In a cohort of 50,282 pregnancies 19 children with cardiovascular defects were born to 1042 women who received female hormones during early pregnancy (18.2 per 1000). Among 49,240 children not exposed in utero to these agents there were 385 with cardiovascular malformations (7.8 per 1000). Six children with cardiovascular defects were born to a sub-

group of 278 women who used oral contraceptives during early pregnancy (21.5 per 1000). After the data were controlled for a wide variety of potentially confounding factors by multivariate methods, the association between in utero exposure to female hormones and cardiovascular birth defects was statistically significant ($P < 0.05$). (N Engl J Med 296:67-70, 1977)

IN 1973 it was suggested that transposition of the great vessels may develop in the fetus if a woman is treated with female sex hormones during early pregnancy.¹ Subsequently, suspicions were raised that antenatal exposure to these compounds might also result in other truncoconal malformations of the heart.² Other cardiovascular anomalies have recently been reported to occur in excess when the infant has been exposed to estrogens and progestogens before birth.³⁻⁵ In this report, the association between antenatal exposure to female sex hormones and cardiovascular birth defects is further evaluated.

MATERIALS AND METHODS

The data were obtained from a prospective cohort study, the Collaborative Perinatal Project, which has been described in detail.^{6,7} A cohort of 50,282 mother-child pairs, seen in 12 hospitals throughout the United States, was selected for study. Pregnant women were recruited between 1958 and 1965. Extensive information on drugs taken during pregnancy, maternal illnesses, complications of pregnancy and other factors was collected before the birth of the child. Data on drug use were recorded at each antenatal visit, and confirmed, with few exceptions, by the attending physician or by review of the hospital or clinic record.

At registration into the study, the mean age of the gravidas was 24 years, and the average interval from conception to the first antenatal visit was approximately 19 to 20 weeks; 48 per cent of the mothers were black, 45 per cent white, and 7 per cent Puerto Rican. The mean birth weight of the offspring was 3130 g; 95.5 per cent of the children were alive after an average follow-up period of four years.

Full details concerning the diagnoses of cardiovascular defects in the children have been published elsewhere.⁶ The defects were ascertained from one or more of the following sources: daily examinations during the first week of life; physical examinations at one year; supplementary data solicited, when applicable, from non-study physicians and hospitals at four, eight, 12, 18 and 24 months of age; and autopsy data. Autopsy data were available up to the fourth birthday for the entire cohort, and for a segment that had been registered during the earlier years of the study, for longer. Autopsies were carried out in 81 per cent of the children who died; 91 per cent of the surviving children attended the one-year examination.

The data on cardiovascular defects were among the most accu-

rately and completely ascertained in the study. Among the surviving children, over 90 per cent of those with cardiovascular lesions, as well as those who were even suspected of having cardiac disease, were re-examined by a cardiologist. In over half the confirmed cases the diagnosis was based on cardiac catheterization, cardiac operation or autopsy. The cardiologists and pathologists were unaware of the drugs ingested by the mothers.

Cardiovascular birth defects were observed in 404 children, 41 per cent of whom died. Multiple cardiovascular anomalies were diagnosed in 105 children (26 per cent). The most common single cardiac lesions were ventricular septal defect (109 children, or 27 per cent), atrial septal defect (37 children, or 9 per cent), pulmonic stenosis (34 children, or 8 per cent), and patent ductus arteriosus (29 children, or 7 per cent).

To evaluate use of female sex hormones in relation to cardiovascular birth defects, attention was confined to the first four lunar months of pregnancy. Data on use of oral contraceptives were available not only from routine drug histories but also from detailed contraception histories given by each woman. Female sex hormones were used by 1042 women, of whom 438 (42 per cent) used both estrogens and progestogens (278 in oral contraceptives), 176 (17 per cent) used estrogens exclusively, and 428 (41 per cent) progestogens exclusively.

Overall, the gravidas who used female sex hormones differed from the remainder of the cohort in many characteristics. Table 1 lists some of the differences. Female hormones were used by 3.0 per cent of white women, 1.4 per cent of black women and 0.5 per cent of Puerto Rican women, among whom there were only 17 exposures. Among white and black women, those who were exposed tended to be older, to have a higher parity and to give birth to smaller children. Also, the various characteristics in the women who used female sex hormones differed according to whether the exposure was solely to estrogens, to progestogens or to various combinations of estrogens and progestogens. For these reasons, multivariate methods were used to control the analyses.

A large number of maternal, fetal and other variables, including drugs used any time during the first four lunar months of pregnancy, were examined, one at a time, to isolate factors other than fe-

Table 1. Age, Parity and Birth-Weight Distributions According to Ethnic Group and Female-Sex-Hormone Exposure during Early Pregnancy (First Four Lunar Months).

ETHNIC GROUP	NO. OF MOTHER-CHILD PAIRS	MEAN AGE (YR)	MEAN PARITY	MEAN BIRTH WEIGHT (G)
White (22,811)*:				
Exposed	692 (3.0%)	25.8	2.5	3,089
Not exposed	22,119	24.7	1.9	3,251
Black (24,030):				
Exposed	333 (1.4%)	24.9	3.0	2,919
Not exposed	23,697	23.6	2.5	3,015
Puerto Rican (3,441):				
Exposed	17 (0.5%)	22.7	2.2	3,211
Not exposed	3,424	23.6	2.0	3,113

*Figures in parentheses denote mother-child pairs.

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Supported by a contract (223-75-3036) with the Food and Drug Administration, a contract (NO1-NS-2-2322) with the National Institute of Neurological and Communicative Disorders and Stroke, and a grant from Hoffman-LaRoche, Inc., Nutley, NJ.

male sex hormones related to the risk of congenital cardiovascular defects. Vaginal bleeding during the first, second or third trimester of pregnancy was not associated with this outcome. Some further risk factors, initially associated with cardiovascular defects, were then eliminated after linear discriminant-function analysis, since their effect disappeared in the presence of the concomitant influence of other factors. These factors included history of abortion, stillbirth or neonatal death, duration of pregnancy of less than eight lunar months, and pelvic or abdominal x-ray exposure during pregnancy. Finally, quantitative estimates of the residual influence of exposure to female sex hormones, in the presence of other factors that predicted cardiovascular deformities, were derived by application of a multiple logistic risk function model.^{7,8} The 24 factors ultimately included in the model are listed in Table 2. By use of the model, it was possible to assign to each mother-child pair in the cohort a probability score that represented the risk of a cardiovascular defect. For the mother-child pairs exposed to female hormones,

Table 2. Factors (Other than Drugs) Related to Cardiovascular Defects and Controlled by Multivariate Analysis.

FACTOR
Single umbilical artery
Birth weight <2000 g
Drug-treated maternal diabetes
Thrombophlebitis during pregnancy
Vena-cava syndrome (positional shock)
Hydramnios
Congenital heart disease in prior sibling
Malformation of fingers or toes in prior sibling
Malformation of the head or spine in prior sibling
Bacterial infection in the 2d or 3d trimester
Hematuria during pregnancy*
White & religion other than Protestant or Roman Catholic (mostly Jewish)
Age of mother ≥40 yr
Hemorrhagic shock during pregnancy
Placenta praevia
Chronic hypertension or eclampsia
Weight loss, or failure to gain, during pregnancy
1st entry to the study
Birth order ≥8th
Exposure to rubella in 1st or 2d trimester†
Duration of gestation ≥11 lunar mo
Entry to study during 1st 2 lunar mo of pregnancy
White & placental weight <400 g
Black or Puerto Rican & placental weight <300 g

*≥15 red blood cells/high-power field.
†Mother-child pairs with either frank clinical rubella in mother or congenital rubella syndrome in child were excluded.

summing the probability scores gave an expected number of malformed children if the exposures did not have an effect. The ratio of the number of children actually malformed to the expected number then yielded a relative-risk estimate that was thereby adjusted for the influence of confounding.

Apart from the risk factors considered above, four groups of compounds (phenothiazines, barbiturates, thyroid hormone or thyroxine and theophylline compounds) and two specific drugs (epinephrine and norepinephrine) were associated with cardiovascular defects. For reasons discussed elsewhere⁷ the data by no means justify causal inferences concerning these agents. However, it was necessary to control their potential confounding influence in the evaluation of female hormones. This control was achieved by reanalysis of the relation between female hormones and cardiovascular defects after the four drug groups and the two specific drugs were added to the multiple logistic risk function model.

RESULTS

Among the 1042 children exposed to female sex hormones during early pregnancy, 19 had cardiovascular defects (18.2 per 1000). Among the remainder, the cardiovascular malformation rate was 7.8 per

Table 3. Female Sex Hormones Used in Early Pregnancy (Any Time During First Four Lunar Months) and Cardiovascular Birth Defects.

FEMALE SEX HORMONES	NO. OF MOTHER-CHILD PAIRS	CARDIOVASCULAR MALFORMATIONS		CRUDE RELATIVE RISK
		NO. OF CHILDREN	RATE/1,000	
Exposed	1,042	19	18.2	2.3
Not exposed	49,240	385	7.8	1.0
Totals	50,282	404	8.0	—

1000, giving a crude relative-risk of 2.3 (Table 3). The crude relative risks were similarly elevated among mutually exclusive as well as overlapping subcategories of exposure, varying from 2.1 to 2.8 (Table 4).

The hormonal compounds and times of the exposure, as well as the actual defects in each of the 19 children (10 male and nine female) are listed in Table 5. Because this group was small, it was not possible to evaluate specific associations more rigorously. However, in the entire cohort there were only six children with tricuspid atresia, three of whom were exposed to female sex hormones before birth. Similarly, two out of the 17 children with transposition of the great arteries were exposed. The bulk of the exposures took place in the second or third lunar month of pregnancy.

Small numbers and unstable rates precluded rigorous evaluation of secular trends in relation to exposure during each lunar month of pregnancy. However, the cardiovascular-malformation rate was highest when exposure began or was continued through the second or third lunar months of pregnancy; the rate was not increased when exposure first occurred after the fourth lunar month.

When we controlled the comparisons by contrasting expected numbers derived by use of the multi-

Table 4. Crude and Adjusted Relative Risks of Cardiovascular Birth Defects in Relation to Exposure to Subgroups of Female Sex Hormones in Early Pregnancy.

TYPE OF HORMONE	NO. OF MOTHER-CHILD PAIRS	CARDIOVASCULAR MALFORMATIONS		CRUDE RELATIVE RISK	ADJUSTED RELATIVE RISK
		NO. OF CHILDREN	RATE/1,000		
Estrogens & progestogens*	438	9	20.5	2.6	2.1
Estrogens only*	176	3	17.0	2.2	1.4
Progestogens only*	428	7	16.4	2.1	1.5
Estrogens alone or in combination†	614	12	19.5	2.5	1.9
Progestogens alone or in combination†	866	16	18.5	2.4	1.8
Oral contraceptives†	278	6	21.6	2.8	2.4
No female sex hormones	49,240	385	7.8	1.0	1.0

*Categories mutually exclusive.
†Categories not mutually exclusive.

Table 5. Female Sex Hormones, Lunar Months (LM) of Their Use and Associated Cardiovascular Birth Defects in Offspring.

ESTROGENIC AGENT	LM	PROGESTATIONAL AGENT	LM	DEFECT
Mestranol	2,3,4	Norethynodrel	2,3,4	Isolated ventricular septal defect
Mestranol	1,2	Norethynodrel	1,2	Isolated aortic stenosis
Mestranol	3	Norethynodrel	3	Isolated ductus arteriosus persists
Mestranol	1	Ethynodiol	1	Transposition of greater arteries & ventricular septal defect
Diethylstilbestrol	2,3,4	Progesterone	4	Isolated aortic stenosis
Ethinyl estradiol	3	Norethindrone	3	Ebstein's anomaly & atrial septal defect of secundum type
Ethinyl estradiol	4	Ethisterone	4	Tricuspid atresia & ventricular septal defect
Estrogen n.o.s.*	1	Progestogen n.o.s.	1	Isolated ductus arteriosus
Estrogen n.o.s.	1	Progestogen n.o.s.	1	Tricuspid atresia
Diethylstilbestrol	2,3,4	—	—	Isolated atrial defect of primum type
Diethylstilbestrol	2,3,4	—	—	Transposition of great arteries, ventricular septal defect & aortic stenosis
Dienestrol	4	—	—	Isolated ventricular septal defect
—	—	Progesterone	2,3,4	Isolated ventricular septal defect
—	—	Norethindrone	2	Isolated ventricular septal defect
—	—	Medroxyprogesterone	1,2,3,4	Tricuspid atresia
—	—	Medroxyprogesterone	3,4	Multiple coarctations of pulmonary artery
—	—	Progesterone	1	Isolated aortic stenosis
—	—	Progesterone	4	Tetralogy of Fallot
—	—	Hydroxyprogesterone	4	Double outlet of right ventricle, ventricular septal defect & ductus arteriosus persists
—	—	Norethindrone	3	

*Not otherwise specified.

ple logistic risk function model with those actually observed, the relative-risk estimates were somewhat reduced (Table 4): the ratios of observed to expected numbers of malformed children were 2.1 for combined estrogen and progestogen exposure ($P < 0.05$), and 1.4 for exposure to estrogens only and 1.5 for exposure to progestogens only. The latter two associations were not statistically significant. Exposure to estrogens alone or in combination or to progestogens alone or in combination yielded adjusted relative risks of 1.9 ($P < 0.05$) and 1.8 ($P < 0.05$), respectively. For oral contraceptives, which were a subgroup of combined exposure, the adjusted relative risk was 2.4. This result was not statistically significant.

When expected numbers of children with cardiovascular defects were calculated with the four groups of compounds and two specific drugs included in the multiple logistic model, the associations were virtually unchanged.

The final procedure was to reanalyze the associations when exposures to female hormones were themselves included as risk factors within a further multiple logistic risk function model. When the 438 exposures to combinations of estrogens and progestogens, the 176 exposures to estrogens only, and the 428 exposures to progestogens only — along with the 24 risk factors, the four groups of compounds and the two specific drugs — were all placed simultaneously in a new model, the relative risk for combined exposure with simultaneous control of all the other factors in the model became 2.0 ($P < 0.05$). This result compares with an adjusted relative risk of 2.1, on the basis of observed and expected numbers (Table 4). In the same model, the relative risk for exposure to es-

trogens only decreased to 1.2 (on the basis of only three exposed and malformed children), whereas the relative risk for exposure to progestogens only was unchanged at 1.5.

DISCUSSION

The findings in this study agree with previous reports¹⁻⁵ and provide further evidence that female hormones taken in the early stages of pregnancy may disturb the normal cardiovascular development of the fetus. Both estrogens and progestogens were associated with the occurrence of congenital heart disease in the offspring, but, because of overlap, there were insufficient data to assess their separate effects adequately.

Earlier reports of similar associations have been based on small numbers. It is possible that only positive findings were reported, so that the accumulated literature gives a rather biased perspective. However, in one respect the results have been consistent in that transposition and other truncocoanal anomalies were common lesions. Such an occurrence was also true tested in the current study.

Drug use was recorded before the birth of the child, and the diagnosis of congenital heart disease was made without knowledge of drug exposure. Observer bias was thus unlikely. To the extent that there may have been failure to record exposure to female hormones because of loss of recall by late registrants into the study, the true association was likely to have been stronger than the one recorded here.

A large number of potentially confounding factors were controlled. Diabetes mellitus, for example, was a risk factor for cardiovascular malformations, and gravidas with the disease were frequently treated with

the female sex hormones. Although adjustment for confounding tended to reduce the strength of the unadjusted estimates of association, the relative risks remained appreciably elevated for the larger exposure groups. Although there may have been further factors of relevance that were not taken into account, a suspicion that the association is causal is strengthened for a number of reasons. Oral contraceptives are usually taken for indications other than disease. Although the data are limited, the association with oral contraceptives was the least affected when potential confounding was controlled. Also, the association was present for exposure to female sex hormones during early pregnancy, particularly during the second and third lunar months, when the heart develops rapidly; exposure first recorded after the fourth lunar month gave no evidence of association with congenital heart disease.

The hypothesis that the use of female sex hormones in pregnancy may cause congenital heart disease must be confirmed in further studies. The sepa-

rate and combined roles of estrogenic and progestational agents need to be clarified, and it is particularly important to evaluate the effect of inadvertent use of oral contraceptives after conception.

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LONG-TERM THERAPY OF MYOCLONUS AND OTHER NEUROLOGIC DISORDERS WITH L-5-HYDROXYTRYPTOPHAN AND CARBIDOPA

MELVIN H. VAN WOERT, M.D., DAVID ROSENBAUM, M.D., JOHN HOWIESON, M.D.,
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Abstract We evaluated the therapeutic effect of L-5-hydroxytryptophan (L-5HTP), the precursor of serotonin (5-hydroxytryptamine), combined with carbidopa, a peripheral decarboxylase inhibitor, in patients with intention myoclonus and examined the serotonin metabolites in spinal fluid, blood and urine before and during therapy. In 18 patients with intention myoclonus due to anoxia or other brain damage, 11 derived more than 50 per cent overall improvement during treatment with L-5HTP and carbidopa. Spinal-fluid 5-hydroxyindoleacetic acid

was 35 per cent lower in patients with intention myoclonus than in controls ($P < 0.05$). Therapy with L-5HTP and carbidopa increased the concentration of serotonin metabolites in urine and spinal fluid.

We postulate that a deficiency of brain serotonin is causally related to intention myoclonus and that the therapeutic effect of L-5HTP and carbidopa may be due to the repletion of serotonin in regions of the brain where serotonergic neurons have degenerated. (*N Engl J Med* 296:70-75, 1977)

THERE have been several clinical investigations demonstrating the effectiveness of L-5-hydroxytryptophan (L-5HTP), the precursor of serotonin (5-hydroxytryptamine), in combination with carbidopa, an extracerebral decarboxylase inhibitor, for the therapy of post-anoxic intention myoclonus.¹⁻³ As shown in Figure 1, serotonin is formed from the essential amino acid tryptophan by, first, its hydroxylation to

L-5HTP and then decarboxylation of L-5HTP to serotonin. The peripheral L-aromatic amino acid decarboxylase inhibitor, carbidopa, prevents the conversion of L-5HTP to serotonin outside the brain and thereby increases serotonin synthesis from L-5HTP in the central nervous system while at the same time decreasing the pharmacologic effects of serotonin in the periphery. The major catabolite of serotonin is 5-hydroxyindoleacetic acid (5-HIAA).

The demonstration of a decreased concentration of cerebrospinal-fluid 5-HIAA in patients with post-anoxic intention myoclonus supported our hypothesis that this disease might be causally related to a deficiency of brain serotonin.¹ We postulated that anoxic brain damage might cause preferential degeneration of serotonergic neurons, thereby reducing brain serotonin formation, and that L-5HTP with carbidopa reduced myoclonic movements by restoring brain se-

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Presented in part at a meeting of the American Academy of Neurology, Toronto, ON, Canada, April 30, 1976.

Supported by a grant (NS 12341) from the National Institutes of Health and in part by a grant (RR 00071) from the Division of Research Resources, General Clinical Research Center Branch.

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MULTIPLE HEPATITIS VIRUSES IN MULTIPLE ATTACKS OF ACUTE VIRAL HEPATITIS

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Abstract We evaluated the causes of 30 episodes of acute viral hepatitis in 13 patients who had multiple attacks. Two (seven per cent) of 30 bouts were caused by hepatitis A virus, and 12 (40 per cent) by hepatitis B virus. No patient, however, had more than one attack with the serologic characteristics of Type A or Type B disease. Thus, there were 16 bouts (53 per cent) not attributable to either of the two recognized hepatitis viruses. None of these "non-

A, non-B" episodes, evaluated for infectious mononucleosis and cytomegalovirus infection, could be ascribed to either. From this evidence, therefore, it appears that the clinical syndrome of viral hepatitis is produced not only by the two viruses (hepatitis A virus and hepatitis B virus) recognized since the 1940's but also, in all probability, by two non-A, non-B agents. (*N Engl J Med* 296:75-78, 1977)

PATIENTS seen during two episodes of acute viral hepatitis usually have one bout identifiable as Type B hepatitis.¹ The sensitive procedures now available for identifying both type-specific surface antigen (HB_s Ag) and the corresponding antibody (anti-HB_s), however, have permitted no more than one of the two bouts to be attributed to hepatitis B virus. The "non-B" episode in a person with two attacks, therefore, is usually assumed to be Type A hepatitis, even though the epidemiologic background may not suggest that etiologic form.²

Since 1956, occasional patients have been observed to have three separate episodes of viral hepatitis,^{3,4} and, recently, as many as four (Karvountzis GG, Mosley JW, Redeker AG: unpublished data). The causation of these "extra" episodes has been conjectural. Well characterized agents besides hepatitis A and B viruses sometimes simulate the syndrome produced by these viruses,⁵ and could account for the multiple bouts. Infectious mononucleosis is the most likely disease to mimic viral hepatitis if hepatic involvement is pronounced and usual features such as sore throat and persistent fever are absent. Other viruses found in the United States may cause clinical hepatitis, but that occurrence is probably rare. Many

of the associations reported in the literature probably represent recovery of latent agents, or an infection occurring coincidentally with hepatitis A or B virus.⁶

These assumptions and unanswered questions about the cause of non-B episodes deserve re-exploration now that Type A hepatitis can be specifically diagnosed by serologic procedures. To do so, we have used the technic of immune electron microscopy in which particulate antigen (hepatitis A antigen) occurring in the feces during Type A disease is agglutinated by an antibody appearing in convalescence.⁷ From the results, we have gauged the extent to which hepatitis A virus is responsible for non-B illnesses in patients with more than one attack.

METHODS AND MATERIALS

Patient Population

Each year since 1969, the Liver Service of John Wesley County Hospital has had 684 to 1157 adult admissions for viral hepatitis, representing approximately 24 per cent of all cases reported in Los Angeles County for that period and 9 per cent of all cases reported in California. This large experience provided a number of cases in which persons were readmitted to the hospital with a second, third or fourth episode of what appeared to be acute hepatitis. Under the supervision of Dr. Robert L. Peters, Department of Pathology, University of Southern California, specimens from all such patients were tested during each admission for HB_s Ag by techniques current at the time.⁸ In most cases, at least small aliquots of serum from these patients remained from specimens routinely collected and stored. When patients were readmitted to the hospital with additional bouts of hepatitis, larger amounts of serum were routinely

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stored at the time of each subsequent episode. Serum samples were also collected and stored when such patients were seen in the Hepatitis Clinic for follow-up visits.

Patients with two or more attacks of acute disease were selected for the present study entirely on the basis of availability of representative serum for both bouts (10 patients), three of three bouts (patient A), four of four bouts (patient B), and three of four bouts (patient C). Thus, the study included 13 patients who were observed during 30 bouts; one of the 13 had a first bout that could not be evaluated serologically.

During the first episode, the highest observed serum bilirubin value had a mean ($\pm$ S.D.) of 8.5 ± 6.4 mg per deciliter, and a median of 7.5 (range, 1.7 to 24.2). The highest serum alanine aminotransferase (glutamic pyruvic transaminase) had a mean of 1590 ± 893 Karmen units and a median of 1340 (range, 500 to 3900). During the second episode, the highest observed serum bilirubin had a mean of 5.8 ± 4.2 , and a median of 5.1 (range, 1.3 to 13.8). The highest serum alanine aminotransferase had a mean of 1794 ± 850 and a median of 1740 (range, 398 to 3420). Student's *t*-test for both unpaired and paired values showed no significant differences (in all comparisons $P > 0.10$).

In the third episode, serum bilirubin and alanine aminotransferase levels were 1.3 and 1260 for patient A, 1.5 and 1350 for patient B and 3.6 and 2160 for patient C. In the two fourth episodes, these indexes were 10.4 and 2520 for patient B, and 6.7 and 1830 for patient C.

Between episodes each patient was clinically well and, if seen in the Hepatitis Clinic, had normal aminotransferase levels on one or more occasions. Liver biopsies were not routinely performed during first episodes, but were available for four of the 13. They were carried out during 11 of the 13 second episodes and all third and fourth bouts. For all biopsies obtained, the pathological diagnosis was acute viral hepatitis.

The ages of the 13 patients at the time of their first episode ranged from 17 to 34 years, with a median of 23. No patient was receiving any medication likely to be responsible for the episode. Ten of the 13 had practiced illicit self-injection at some time in their lives; three consistently denied drug abuse. Nineteen of the 30 episodes evaluated were preceded by admitted illicit self-injection within six months. Two were associated with contact with persons practicing illicit self-injection, one was related to contact with hepatitis known to be HB_s Ag-negative, and eight followed no obvious source or mechanism of exposure.

Antibody to Hepatitis A Virus

Serum specimens were tested for antibody to hepatitis A antigen by immune electron microscopy as previously described.⁷ Specimens were randomized, coded, and placed in sets containing a number of specimens that could be conveniently tested at one time. All serums from the same patient were tested as part of the same set, but each set contained serums from more than one patient. Antibody was evaluated in the coded samples by means of a semi-quantitative scoring system of 0 to 4+ as previously described.⁷ This technic has been shown to be sensitive and reliable for detecting serologic responses to the antigen as compared to other available methods.⁹

Tests for Hepatitis B Virus

All serum specimens were re-tested for HB_s Ag by radioimmunoassay (Ausria, Abbott Laboratories)¹⁰ and for confirmation of specificity when positive.¹¹ The test for anti-HB_s was passive hemagglutination,¹² commercially available materials (Electro-Nucleonics Laboratories, Incorporated) being used. In the procedure, cells coated with both HB_s Ag/adw and HB_s Ag/ayw were used after sensitivity and specificity had been checked against internal laboratory standards. Antibody to the core antigen (HB_c Ag) of hepatitis B virus was assayed by blocking in a micro-solid-phase radioimmunoassay.¹³ Results for this antibody have been expressed semi-quantitatively on a scale of 0 to 2+ on the basis of proportionate reduction in binding of reagent HB_c Ag.

Evaluation for Other Causes

Clinical (sore throat, lymphadenopathy, unusual splenomegaly), hematologic (proportion of atypical lymphocytes) and serologic (heterophil antibody, by Mono-Test, Wampole Laboratories) evaluation for infectious mononucleosis was routinely performed at the time of every admission. Antibodies to cytomegalovirus were tested by a standard complement-fixation procedure.¹⁴

RESULTS

Two Bouts

Ten patients had two bouts of acute viral hepatitis. Hepatitis B virus could not be serologically implicated as responsible for both episodes in any person. It was, however, the cause of one of two bouts in nine of the 10. All nine had HB_s Ag positivity during the acute phase of the Type B illness, and a specific relation to that episode was evidenced by lack of persistent HB_s Ag positivity in convalescence.¹⁵ The 10th patient, who was unaware of clinical hepatitis before his first admission, had an anti-HB_s titer of 1:256 that persisted without significant subsequent change. He was HB_s Ag-negative during both admissions. None of the serologic indexes, therefore, suggested that either of his two episodes was Type B hepatitis.

Table 1 shows the occurrence and pattern of antibody to hepatitis A by immune electron microscopy in these 10 patients. Five had antibody to hepatitis A consistently absent, indicating no experience with the agent before or during the period of observation. Four other patients had the antibody at an unchanging titer throughout the acute and convalescent phases of both illnesses, indicating prior immunity and no reinfection. One patient, however, did experience a diagnostic increase in antibody as a consequence of his first illness. This 21-year-old man (the "10th" patient discussed above) had contact with HB_s Ag-negative hepatitis one month before his first bout. His second illness, which was eight months later, was not related serologically to hepatitis A or B infection.

Three and Four Bouts

Findings in three patients with three or four bouts are summarized in Table 2.

Table 1. Patterns of Antibody to Hepatitis A Virus (Anti-HA) in 10 Patients with Two Episodes of Acute Viral Hepatitis.

SEROLOGIC CHARACTERIZATION FOR TYPE B HEPATITIS	PATIENTS STUDIED	ANTI-HA PATTERN		
		CONSISTENTLY ABSENT	PRESENT AT UNCHANGING TITER	APPEARANCE OR INCREASE IN TITER
Both bouts Type B	—	—	—	—
1st bout Type B 2d bout "non-B"	6	4	2	—
1st bout "non-B" 2d bout Type B	3	1	2	—
Neither bout Type B	1	—	—	1

that we have described in this report. In the first place, each episode was a distinct departure from good health, and was accompanied by typical prodromes of acute viral hepatitis. Although chronic hepatitis occasionally simulates acute disease, it rarely does so repeatedly.²¹ Secondly, all biopsies in later episodes were interpreted as acute hepatitis, without evidence of chronicity. Thirdly, there was no statistically significant change in serologic indexes of hepatitis A or B virus during "non-A, non-B" episodes, making resurgence of a chronic infection by either seem very unlikely. Fourthly, the serologically identifiable episodes did not necessarily precede the unidentified ones. This lack of a necessary or fixed etiologic sequence in the identifiable bouts argues against relapse of Type A or Type B hepatitis as an explanation for those episodes subsequent to the first. Fifthly, multiple bouts are most commonly seen in persons practicing illicit self-injection, which is to be expected from the range and intensity of their exposures. Some investigators have objected that persons with extensive needs for transfusion, such as those with hemophilia, should have a comparable risk of multiple attacks if the episodes were due to hepatitis viruses. Every shared "fix," however, exposes the illicit drug user to one or more other potentially infective drug users. Even if a blood-collection agency were extremely negligent, no chronic recipient would be exposed to blood donated entirely from addicts. Furthermore, many persons needing frequent transfusions because of bleeding disorders have onset of that requirement in childhood, when hepatitis viruses are more likely to produce subclinical infection.

In view of these considerations, we believe that the serologic evidence concerning our 13 patients strengthens the already considerable evidence for a "third" non-A, non-B virus of human hepatitis, and suggests a "fourth" agent, immunologically distinct from the third.

We are indebted to Miss Virginia Edwards and Mrs. Margaret Jones for finding and assembling the specimens for testing and to Mr. Jose Valdesuso and Mrs. Doris Wong for technical assistance.

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Table 2. Serologic Evaluation of Three Patients with Three or Four Separate Episodes of Acute Viral Hepatitis.

PATIENT	STATUS WHEN OBSERVED	DATE (Mo/Yr)	ANTIBODY TO HEPATITIS A*	HB _s AG	ANTI-HB _s †	ANTI-HB _c ‡	ANTIBODY TO CYTOMEGALOVIRUS‡	EVALUATION
A	1st bout	11/71	(-)	(-)	(-)	(-)	16	"Non-A, non-B"
	Follow-up	12/72	(-)	(-)	(-)	(-)	16	
	2d bout	3/72	(-)	+	(-)	±	16	Type B
	Follow-up	5/72	(-)	+	(-)	1+	32	
	3d bout	12/72	(-)	(-)	128	2+	128	"Non-A, non-B"
	Follow-up	1/73	(-)	(-)	256	2+	64	
B	1st bout	6/71	(-)	(-)	(-)	(-)	8	Type B
	Follow-up	7/71	(-)	(-)	(-)	+	8	
	2d bout	8/71	(-)	(-)	32	2+	4	"Non-A, non-B"
	Follow-up	10/71	(-)	(-)	32	2+	AC§	
	3d bout	4/72	(-)	(-)	64	2+	8	Type A
	4th bout	4/73	2-3+	(-)	16	2+	(-)	
	Follow-up	5/73	3+	(-)	32	2+	16	"Non-A, non-B"
C	1st bout	5/68	NT¶	NT	NT	NT	NT	Not studied
	2d bout	5/70	NT	+	NT	NT	NT	
	Follow-up	10/70	(-)	(-)	16	2+	(-)	Type B
	3d bout	11/71	(-)	(-)	32	2+	(-)	
	Follow-up	2/72	(-)	(-)	(-)	2+	(-)	"Non-A, non-B"
	4th bout	6/72	(-)	(-)	(-)	2+	(-)	
	Follow-up	7/72	(-)	(-)	(-)	1+	(-)	"Non-A, non-B"

*Quantity of antibody on a scale of 0-4+ as judged by immune electron microscopy.

‡Quantity of antibody on a scale of 0-2+ as judged by radioimmunoassay blocking.

§Anti-complementary.

†Reciprocal titer.

¶Not tested.

Patient A had a second episode characterized as Type B hepatitis on the basis of HB_s Ag positivity, as well as the patterns of anti-HB_s and anti-HB_c. Neither of two other bouts, however, could be identified etiologically.

Patient B had her first bout characterized as Type B hepatitis on the basis of the patterns of anti-HB_s and anti-HB_c, and a third bout characterized as Type A hepatitis by the subsequent appearance of antibody. The latter followed by one month what she stated was the only use of her husband's syringe and needle within the six-month interval before that illness. Patient B's second and fourth bouts remained etiologically unexplained.

Patient C had his first bout before HB_s Ag testing was introduced, and serum was not available for subsequent study. The second bout was characterized as Type B hepatitis by HB_s Ag positivity, and the patterns of anti-HB_s and anti-HB_c. Neither the third nor fourth attacks, however, could be characterized.

Other Serologic Data

None of the 13 patients had evidence of infectious mononucleosis associated with any episode of acute hepatitis. None of three patients with 10 bouts studied for cytomegalovirus had a serologic indication of hepatitis caused by that agent (Table 2).

DISCUSSION

Twelve of the 13 patients in this series had evidence that hepatitis B virus was etiologically associated with one of multiple episodes of acute viral hepatitis. Only two patients, however, had serologic findings to indicate that one of their multiple episodes was Type A hepatitis. Thus, Type A hepatitis was rela-

tively uncommon (two of 30) as a cause of sporadic viral hepatitis among this group of adults, even those experiencing two or more attacks.

The ability to make a specific diagnosis in cases of Type A as well as Type B hepatitis is identifying an ever larger group of episodes of acute icteric hepatitis for which the only accurate designation at present is "non-A, non-B." One explanation for their occurrence, of course, would be inadequacy of presently available serologic methods. For Type B hepatitis that possibility seems remote, because of the sensitivity of tests for HB_s Ag, anti-HB_s, and anti-HB_c. For Type A hepatitis, the proportion of cases potentially missed when immune electron microscopy is used for detection of antibody to that type is unknown. Experience in one common-vehicle epidemic, however, suggested that essentially all overt infections (25 of 25) were documented by this technic.¹⁶ This conclusion is supported by unpublished data from another food-borne outbreak¹⁷ (24 of 24 [Maynard JE: personal communication]). Direct comparison of immune electron microscopy with other technics for identifying hepatitis A antibody showed comparable sensitivity.⁹

The present data extend the previous suggestions from epidemiologic¹⁸ and serologic^{19,20} studies of transfusion-associated hepatitis that there is one additional, previously unrecognized hepatitis virus. Patients A, B and C (Table 2), however, had a pattern of acute attacks compatible with two "new" agents.

An alternative explanation to the hypothesis of other, immunologically distinctive agents would be clinical recurrences of a chronic infection. Several circumstances, however, suggest that recurrence of an initial infection is inadequate as the only explanation for the multiple, etiologically unidentifiable illnesses

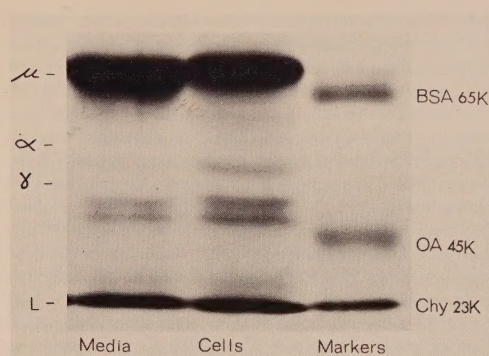


Figure 1. Immunoglobulin Synthesis in Vitro.

Polyacrylamide-gel electrophoresis of radiolabeled immunoglobulin (Ig) that was produced in vitro and subsequently reduced to light and heavy chain is shown. Secreted Ig (media) and intracellular Ig (cells) were analyzed separately. The symbols on the left side show the electrophoretic position for μ chains, α chains, γ chains and light (L) chains. Markers consisted of ^{125}I -labeled bovine serum albumin (BSA, molecular weight of 65,000 daltons), ovalbumin (OA, molecular weight of 45,000 daltons) and chymotrypsin (Chy, molecular weight of 23,000 daltons).

kylated and subjected to electrophoresis on 7.5 per cent polyacrylamide slab gels. This analysis demonstrated that the immunoglobulin produced in vitro consisted of μ and light chains (Fig. 1).

DISCUSSION

Leukemic reticuloendotheliosis, or hairy-cell leukemia, is a well described clinical syndrome.¹⁻⁴ Although a wealth of information is available on this disease, the nature of the hairy cell remains incompletely understood in terms of the cell line from which it derives. Whereas the weight of evidence seems to favor a lymphocytic origin of these cells,⁶⁻⁹ there is evidence that the hairy cells have some properties of cells of the mononuclear phagocyte line.¹⁰⁻¹² The case presented above provided an unusual opportunity to observe the longitudinal development of a pathological process spanning the spectrum between chronic lymphocytic leukemia with monoclonal IgM synthesis and hairy-cell leukemia. It also provided the opportunity to demonstrate that B lymphocytes with characteristics of hairy cells could produce monoclonal IgM in vitro.

The patient acquired what might best be characterized as benign monoclonal gammopathy approximately 17 years before the development of an obviously neoplastic process involving lymphoid cells. The clinical presentation was consistent with hairy-cell

leukemia, although the peripheral white-cell count was somewhat high and the degree of anemia perhaps more marked than that normally seen.¹ The neoplastic cells were shown to be of the B-lymphocyte lineage by receptor studies, membrane and cytoplasmic immunofluorescence and synthesis of monoclonal IgM in vitro. Approximately 1 per cent of the total protein produced in vitro was immunoglobulin, suggesting a degree of cellular maturation intermediate between chronic lymphocytic leukemia (0.5 per cent) and myeloma (5 per cent). In addition, there was monoclonal IgM production in vivo. The neoplastic cells had the morphology of hairy cells in terms of the numerous surface microvilli. More importantly, they contained large quantities of tartrate-resistant acid phosphatase, which was demonstrated to be isozyme 5 by acrylamide electrophoresis.

We believe that hairy-cell leukemia is usually a B-lymphocyte neoplasm deriving from a cell genetically expressing isozyme 5 of acid phosphatase. On occasion this clone may express its genetic capacity for synthesis of immunoglobulin.^{8,9} The case described demonstrates the clonal origin of hairy-cell leukemia in terms of both macroglobulin and enzyme synthesis.

We are indebted to Shirley G. Quan for technical assistance and to Dr. Robert I. Lehrer for the acid phosphatase isozyme studies.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL



Weekly Clinicopathological Exercises

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Continued preparation of these Case Records has been made possible by a generous grant from Pfizer Pharmaceuticals to the Massachusetts General Hospital.

CASE 2-1977

PRESENTATION OF CASE

A 32-year-old man was admitted to the Massachusetts Eye and Ear Infirmary because of a cervical mass.

He was well until two months previously, when a left-sided earache developed and was treated with penicillin followed by cephalexin. After two weeks the earache improved, but he began to have pain and stiffness in the left side of the neck, accompanied by local swelling. Further doses of antibiotics were given, without benefit. Six days before admission he came to the hospital, where he was found to have diffuse enlargement of a nontender thyroid gland, with shotty cervical lymph nodes and a tender lymph node, 2 cm in diameter, in the left submandibular triangle. There was an erythematous macular rash on the left side of the neck. The liver and spleen were not palpable. The hematocrit was 41.8 per cent; the white-cell count was 6800, with a normal differential count. The erythrocyte sedimentation rate was 10 mm per hour. A screening test for infectious mononucleosis was negative.

Two days before entry skin tests were administered for mumps, histoplasmosis, coccidioidomycosis and tuberculosis. On the day of admission he returned for interpretation of the skin tests, all of which were negative. He complained of hoarseness during the preceding 36 hours, and indirect laryngoscopic examination disclosed paralysis of the left vocal cord in abduction. There was a questionable further increase in the size of the thyroid gland.

An eruption had been observed in the mouth when the patient was eight weeks of age. At three months he

entered another hospital, where swelling of the palate with necrosis was observed. At the age of eight months measles occurred, followed by chronic discharge from both ear canals, a scaling eruption of the scalp and an erythematous eruption on the trunk, in the axillary and inguinal regions and behind both ears. At 19 months of age he was seen at another hospital, where x-ray films were reported to show extensive destruction of both mastoid processes and lesions in the mandible and palate; the remaining bones of the skull and the other bones appeared normal. Biopsies of the palate and an ear canal disclosed granulation tissue, and antibiotics and local measures were given, without improvement. At the age of three years he was examined at another hospital. X-ray studies showed irregular destruction of the left mandible, with lesions in the maxilla, temporal bones, sphenoid bone and base of the sella turcica and a single large lesion in the mid-diaphysis of the left femur; the lungs appeared normal. Biopsy of the femoral lesion was reported to reveal eosinophilic granuloma, and a review of previous biopsy specimens led to the same diagnosis. Radiation therapy was given to the right and left sphenoid and temporal regions, the mandible and the left femur. The patient gradually improved but required further radiation treatment at the age of four years. He underwent dilatation of both ear canals as well as orthodontic treatment to improve the shape of the mandible.

There was a past history of infectious mononucleosis and mumps. His mother had been treated for a hypoactive thyroid gland. There was no history of fever, chills, sweats, weight loss, dysphagia, regurgitation, thyroid tenderness or symptoms of hyperthyroidism or hypothyroidism.

The temperature was 36.7°C, the pulse 70, and the respirations 20. The blood pressure was 130/75 mm Hg.

On examination the patient appeared well. The palate was high and arched, and the left maxilla was depressed. The thyroid gland was diffusely enlarged, hard and nontender, and a diastolic bruit was heard over the right lobe; the left lobe was larger than the right. Multiple shotty left cervical, left supraclavicular and bilateral axillary lymph nodes and a left submandibular lymph node, 1.5 cm in diameter, were palpable. The lungs, heart and abdomen were normal. There was no peripheral edema. Neurologic examination was negative.

The urine was normal. The hematocrit was 43.3 per cent; the white-cell count was 6400, with 65 per cent neutrophils, 29 per cent lymphocytes, 5 per cent monocytes and 1 per cent eosinophils. The erythrocyte sedimentation rate was 18 mm per hour. The urea nitrogen was 15 mg, the glucose 88 mg, the calcium 9.7 mg, the phosphorus 3.5 mg, the cholesterol 217 mg, the bilirubin 0.9 mg, the uric acid 2.5 mg, and the protein 6.8 g (the albumin 4.7 g, and the globulin 2.1 g) per 100 ml. The free thyroxine was 2.4 ng, the total thyroxine 11µg, and the total tri-iodothyronine 130 ng per 100 ml (normal, 75 to 190 ng). The lactic

dehydrogenase (LDH) was 70 U (normal, 34 to 76 U), the creatine phosphokinase (CPK) 32 U (normal, 0 to 60 U), and the alkaline phosphatase 28 U (normal, 10 to 42 U). An x-ray film of the chest was normal. Tomographic examination of both lungs disclosed no evidence of metastatic tumor. X-ray films of the paranasal sinuses revealed that both maxillary sinuses were slightly smaller than average, but all the sinuses were well pneumatized and appeared normal. Panorax dental films of the mandible and maxilla showed no bony lesion. Radiographic examination of the larynx (Fig. 1) disclosed paralysis of the left true vocal cord, with asymmetry of the ventricles; the subglottic area appeared normal, and no mass was seen. Films of the neck (Fig. 2) disclosed a soft-tissue mass, 3 by 5 cm, in the subcricoid pretracheal region. A barium-swallow examination demonstrated that the esophagus was normal; slight aspiration of barium occurred on swallowing. Films of the skull revealed that the pituitary fossa was very shallow; the anterior and posterior clinoids appeared normal, and the floor of the sella was intact; the apexes of the petrous bones were higher than usual, consistent with basilar impression; the internal auditory canals were normal; the

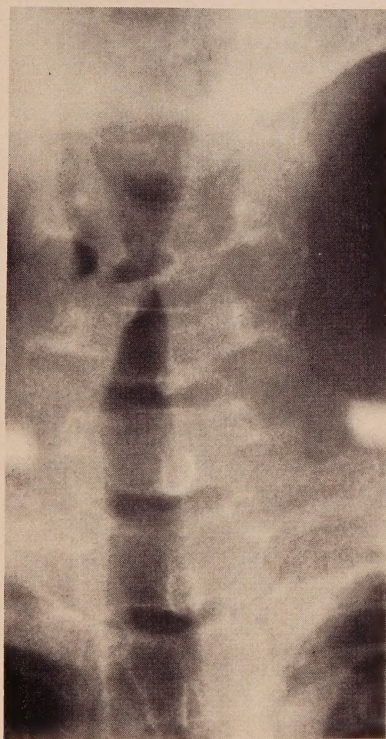


Figure 1. Frontal Radiograph of the Larynx, Showing Abduction and Atrophy of the Left Vocal Cord with Deformity of the Laryngeal Ventricle Consistent with Vocal-Cord Paralysis.

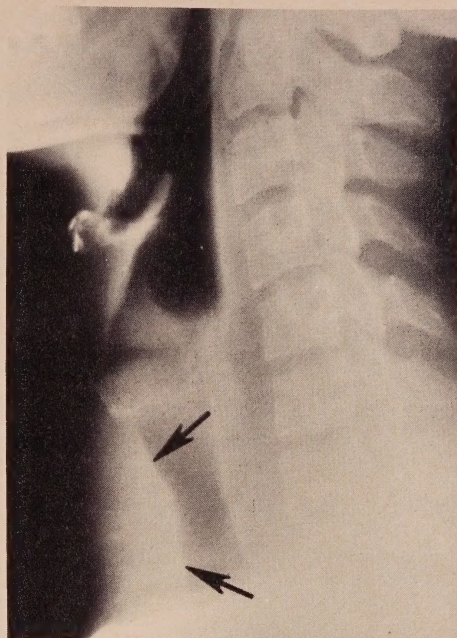


Figure 2. Lateral Film of the Neck, Showing a Pretracheal Soft-Tissue Mass (Arrows) Indenting the Anterior Tracheal Wall.

No calcification is visible in the mass.

mastoid air cells were poorly developed and poorly pneumatized bilaterally. Tomographic sections of the petrous bone showed no erosion. A ^{99m}Tc diphosphonate bone scan was normal. A test for rheumatoid factor was positive; an L.E.-cell test and a test for antinuclear antibodies were negative. Serum immunoelectrophoresis and agarose-gel electrophoresis were normal. An attempted thyroid scan was unsatisfactory because the patient vomited after ingesting the tracer dose; the 24-hour uptake of radioactive iodine was 0.7 per cent. A test for antibody to colloidal antigen was strongly positive; a test for antibody to microsomal antigen was negative. An audiographic test revealed high-frequency loss in the left ear and a small conductive loss in both ears; there was tone decay in the left ear at 6000 Hz.

Codeine was given for cervical pain. A diagnostic procedure was performed on the fifth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. MARTIN B. LEVENE*: We have the problem of a 32-year-old man with a rapidly enlarging thyroid gland associated with neck pain and stiffness and the development of paralysis of the left vocal cord shortly before admission. Of considerable interest and prob-

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able importance is the history of radiation therapy to multiple sites, including several areas in the region of the head and neck, in early childhood. Before proceeding with the discussion, we should view the pertinent x-ray films.

DR. ALFRED L. WEBER: On a film of the skull the sella appears well corticated but somewhat shallow. The mastoids are poorly pneumatized, but there is no evidence of a destructive process, either within them or in the remainder of the temporal bones. There is platybasia with elevation of the petrous pyramids, but this finding is of no importance. Laminagraphic study of the temporal bones revealed no area of destruction. On special views both jugular foramina are of normal size, although the left side is smaller than the right. The adjacent visualized structures, including the occipital condyles, the hypoglossal canal, the basisphenoid and basiocciput are normal. Films of the mandible reveal no abnormality. The lateral view of the neck (Fig. 2) demonstrates a homogeneous soft-tissue mass in the lower portion anterior to the trachea, which is slightly indented anteriorly and on the left side but is sharply defined, without narrowing or invasion. The mass contains no foci of calcification. The prevertebral soft tissues are normal in width. The plain film and laminagrams of the larynx (Fig. 1) reveal atrophy of the left true and false cords. The fluoroscopist observed limited adduction and abduction in keeping with paralysis of the left vocal cord. The subglottic air space is normal.

DR. LEVENE: Is the mass in the lower portion of the neck consistent with an enlarged thyroid gland?

DR. WEBER: Yes; it is in the area of the thyroid gland.

DR. LEVENE: It is of great help to know that there is no radiographic evidence of recurrence of the disease of 30 years ago.

The possibilities to be considered in the differential diagnosis may be divided into three categories — infectious thyroiditis, autoimmune thyroiditis and neoplasia. An infectious process, such as acute suppurative thyroiditis or subacute thyroiditis, can be excluded by the absence of local tenderness of the thyroid gland, the lack of fever, the normal white-cell count and differential count and the normal or only slightly elevated erythrocyte sedimentation rate. Disposing of a chronic lymphocytic thyroiditis is somewhat more difficult since I assume that the strongly positive test for antibody to colloidal antigen points in this direction, and the hard, diffusely enlarged, nontender thyroid gland could have resulted from that disease. However, the rapid enlargement of the gland over a period of weeks would be unusual for chronic lymphocytic thyroiditis. The negative test for antibody to microsomal antigen is also helpful in excluding this disorder. The rare entity of invasive (Riedel's) thyroiditis usually involves a single lobe and is slow to develop. It can, however, produce recurrent laryngeal-nerve paralysis with immobilization of the vocal cord.

I find the evidence in favor of a neoplastic process more impressive. The rapid enlargement of the gland, which was hard and nontender, is very suggestive of a poorly differentiated thyroid carcinoma. The paralysis of the left vocal cord indicates involvement of the recurrent laryngeal nerve, which is much more likely to be due to tumor than to any other cause. The abducted position of the vocal cord rather than its usual position in adduction when paralyzed is indicative of a fairly recent onset of the paralysis. As the cord remains paralyzed it gradually drifts into a totally abducted position in most patients. I am not sure what to make of the cervical and axillary lymphadenopathy, which is described as shotty except for the 1.5-cm submandibular lymph node. I suppose that one must think of the possibility of a lymphoma of the thyroid gland, but I choose to believe that the shotty lymph nodes are not an important feature. I must admit that I am influenced by the history of radiation therapy to the head and neck in early childhood. We are given no information about the radiation dosage, but one can surmise that the areas of involvement by eosinophilic granuloma were treated with doses in the range of 600 to 900 rads. The treatment was given to the right and left sphenoid and temporal regions as well as the mandible, and it is possible that the treatment of the mandible resulted in direct irradiation of the thyroid gland. However, even if only scattered radiation reached the thyroid gland it is still conceivable that the dose to the gland exceeded several hundred rads.

In 1950 Duffy and Fitzgerald¹ called attention to nine children with thyroid cancer who had received radiation therapy to the thymus gland and questioned the possibility of a causative relation. Since then numerous studies, including one from this institution,² have confirmed the oncogenic effects of radiation of the region of the head and neck in childhood and to a lesser extent in adult life. Doses to the thyroid gland of 200 to 900 rads are usually implicated. There have been benign lesions, such as single or multiple adenomas and colloid cysts, as well as thyroid cancers. The cancer is almost always papillary or follicular or a mixture of these two types. Undifferentiated cancer is almost never seen. The latent period between the exposure to radiation and the development of thyroid cancer varies greatly and has been reported to be as short as three months and as long as 37 years, with the mean in multiple series just under 10 years.³ A recent report by Favus and his colleagues⁴ gives an idea of the substantial risk associated with head and neck irradiation in the range of 700 to 900 rads, mostly given to children below the age of 12 years. In a group of 1056 patients who had received such irradiation 283, or 27.3 per cent, were found to have nodular thyroid disease by physical examination or scintigrams, or both. Information about the surgical findings was available on 182 of these patients. Thyroid carcinoma was present in a third of them, and the remainder were found to have benign lesions, principally multiple adenomas. The authors

calculated that the risk factor is 4.5 carcinomas per 10^6 subjects per rad per year, and that is in the range of other figures in the literature.

What are the implications of this and similar studies for the hazards associated with irradiation therapy of cancer? This is an important question. After all, the thyroid gland is extensively radiated in children and young adults with Hodgkin's disease. Mole⁶ addressed this issue in the Silvanus Thompson Memorial Lecture. "One notable fact about human and experimental observations is that the frequency per rad of induced cancer decreases once an optimum radiation dose is exceeded. For instance, there is clear evidence that radiotherapy to the pelvis for benign disorders is followed by induced leukemia and induced pelvic cancer, whereas there has been no evidence yet of either after the larger radiation exposures prescribed for the treatment of uterine cancer." Mole's explanation is a simple one. The larger the radiation dose, the fewer cells there are that retain their ability to divide, and cells that are unable to divide cannot form tumors no matter what other cancer-producing propensities they may have acquired.

In regard to the patient under discussion, I believe that the radiation therapy 30 years ago was appropriate and lifesaving. Today, he would be classified as having Hand-Schüller-Christian disease and probably treated with systemic chemotherapy, such as methotrexate and prednisone. I believe that he had a cancer of the thyroid gland, presumably a poorly differentiated type in view of the rapid progression and diffuse enlargement. Admittedly, this is unusual for radiation-induced thyroid cancer, which, as I previously mentioned, is almost always well differentiated.

DR. ELIAS C. DOW: I agree with your impression that the lesion was probably a neoplasm. It is unfortunate that the thyroid scan was not repeated to determine what parts of the thyroid gland were functioning. Incidentally, the uptake of 0.7 per cent was inaccurate if the patient vomited the tracer dose, since one wouldn't know how much radioiodine was absorbed.

DR. GILBERT H. DANIELS: The thyroid gland was very impressive clinically. It was large, stony hard and nontender. The vocal-cord paralysis had developed over a period of days, and we thought that an inflammatory condition was very unlikely. We all believed that the process was a neoplasm, and the question was what type of tumor. We hoped that it would turn out to be a primary lymphoma, which would be the most amenable to treatment.

DR. AUSTIN L. VICKERY, JR.: Dr. Crocker, from the Children's Hospital Medical Center, took care of this man for the initial disease many years ago.

DR. ALLEN C. CROCKER: The terminal course of this man's illness was unnerving for those of us oriented primarily toward the pediatric age group. His disease had its major activity in the middle 1940's. I did not see him then, but in reviewing hospital records of children with histiocytosis I became familiar with his rec-

ord and saw him subsequently, when he reappeared at the age of 16 years. At that time he recalled a few of the comments about his disease that his parents had made but was puzzled and wanted to know its implications for the future. I summarized the data in the record for him, concluding that "the old disease problem represented no further concern, and that he now should be handled normally in all regards." I reassured him that his old battle had been well fought and won. I continued to have contact with him whenever some milestone or question arose. My desire was to help him live free of concern and to counterbalance some of the gloom that is evident in the standard textbooks in the discussion of the histiocytosis syndromes. It was therefore shocking to hear recently that this man was very sick, with a rapidly progressive disease. Thus, the opportunity today to review the whole sequence of the illness is an important one for me, and his course provides an important lesson for the pediatric therapist as he views the problem of histiocytosis.

The category of histiocytosis is characterized by the presence of collections of histiocytes, with other cell types contributing to some extent. The disorder occurs sporadically; we have never seen multiplex involvement in the same family. There is a characteristic age for the development of the lesions, and this young man had the disease in the preschool years, a common time for their appearance. The distribution of the lesions is typical, most commonly within the medulla of bones and next in lymph nodes and the skin. In the majority of the patients it becomes apparent during the first year of observation whether the process is going to become broadly invasive, behaving sometimes like a malignant tumor, or whether the host will succeed in controlling the disease. This patient's illness involved the bone, skin, scalp, ear canals and buccal mucosa and resulted in anemia and lymphadenopathy, but he never had identifiable involvement of the liver, spleen, lungs or meninges around the posterior pituitary gland or hypothalamus, all of which are often affected in other patients.

Dr. Levene was kind to state that the therapy employed, which included transfusion and radiation therapy in the era before antitumor chemotherapy, was appropriate and may have been lifesaving. It may well have modified the course of the disease, but this young man probably did not have a potentially fatal type of involvement. This probability raises a challenging consideration because histiocytosis is one of the half dozen most common indications for radiotherapy for nonfatal disease in children. We are now at a crossroads in decisions about its management. Dr. Greenberger is presently analyzing the large experience with this category of disorder at the Children's Hospital Medical Center and within the next year or two may be able to shed light on the long-term effects of the therapy that has been used.

DR. VICKERY: May we have the medical students' diagnoses, Dr. Slater?

DR. EVE E. SLATER: The students also diagnosed a primary malignant tumor of the thyroid gland. They were unable to specify the histologic type but suggested either an anaplastic carcinoma or a lymphoma with marked invasive properties in view of the rapidly progressive course.

CLINICAL DIAGNOSIS

Tumor of thyroid gland, ? undifferentiated carcinoma or lymphoma.

DR. MARTIN B. LEVENE'S DIAGNOSIS

Poorly differentiated carcinoma of thyroid gland.

PATHOLOGICAL DISCUSSION

DR. VICKERY: A review of the microscopical slides of the femoral-biopsy specimen obtained at the Boston Children's Hospital at the age of three years showed a cellular infiltrate composed largely of histiocytes with some eosinophils. The late Dr. Sidney Farber made a diagnosis of eosinophilic granuloma on the basis of this specimen. The prior biopsy specimens of soft-tissue lesions were reviewed at that time and also interpreted as consistent with eosinophilic granuloma.

The possibility that the patient's current illness was a recurrence of the histiocytosis after a disease-free interval of over 25 years seemed very unlikely to all the consultants. Although eosinophilic granuloma may recur after a long period, an interval of inactivity of this duration with an exclusive appearance in the thyroid gland would be very atypical. The prevailing preoperative opinion was that the patient had a primary malignant tumor of the thyroid gland. Undifferentiated carcinoma of the thyroid gland characteristically afflicts much older patients, usually in the seventh decade. The question of an undifferentiated carcinoma was raised because of the rapid clinical course, which is virtually pathognomonic for that diagnosis, but the age of the patient was considered a very unusual feature. Therefore, largely on the basis of the patient's youth, a malignant lymphoma was considered the more likely diagnosis.

A needle biopsy of the thyroid mass was performed, and examination of the specimen showed a very cellular tumor without recognizable architecture, composed of rather uniform cells with abnormal nuclei and many mitoses (Fig. 3). The picture was not typical of either malignant lymphoma or anaplastic carcinoma of the thyroid gland. We finally made a diagnosis of undifferentiated carcinoma with a suggestion that it might be an unusual form of poorly differentiated follicular carcinoma.

Since the tumor was considered inoperable radiotherapy was administered under the supervision of Dr. Chiu-Chen Wang. Dr. Gunderson, how many rads did the patient receive?

DR. LEONARD L. GUNDERSON: He received a 5731-rad midplane dose delivered to the entire neck, bilateral supraclavicular areas and upper mediastinum

over a four-week period. Since the tumor had been growing rapidly it was decided to deliver a portion of the treatment at two fractions per day instead of the usual single fraction a day. The initial dose of 3714 rads was delivered in 20 fractions over a 15-day period, on 12 of those days at two fractions a day (150 rads per fraction). After a two-week interval of rest some regression of the tumor was observed. An additional 2017 rads was then delivered in 10 daily fractions.

DR. VICKERY: The irradiation resulted in partial relief of the pain and some shrinkage of the mass but less than had been anticipated. Lymph nodes were still palpable in the left side of the neck, and the vocal cord remained paralyzed. A course of doxorubicin hydrochloride was then given but produced little response. His condition gradually deteriorated, with increasing difficulty in swallowing and worsening neck pain. He died at home about four months after the biopsy.

Examination at autopsy disclosed that the thyroid gland was totally replaced by a firm, pale tumor that encircled the trachea like a collar and extended into the surrounding soft tissues (Fig. 4). There were grossly evident metastases to the cervical, mediastinal and bronchial lymph nodes. The pleural surfaces were studded with tumor plaques, and the pleural lymphatics were distended with tumor. Metastatic nodules ranging from 0.5 to 1.5 cm in diameter were present in all the lobes of the lungs. Within the abdomen there were metastases in the liver and para-aortic lymph nodes, and the ribs and vertebrae were also sites of metastatic deposits.

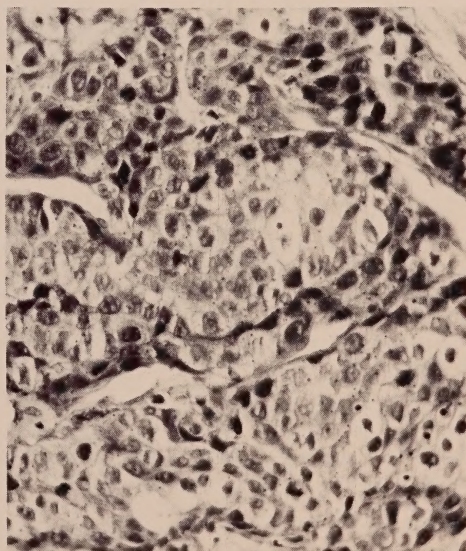


Figure 3. Needle-Biopsy Specimen of the Thyroid Tumor, Showing Solid Clusters of Neoplastic Cells with Atypical Nuclei. ($\times 300$)



Figure 4. Cross-Section of the Mass at the Thyroid Level, Showing Complete Replacement of the Thyroid Gland. The carcinoma obliterated the extrathyroidal soft-tissue landmarks and encased the trachea like a collar.

Microscopical examination of multiple sections from the thyroid gland showed no residual normal parenchyma but massive replacement by tumor, with areas of necrosis and fibrosis. The carcinoma cells were widely infiltrative and, as in the biopsy specimen, displayed no definite arrangement. The radiation undoubtedly produced much necrosis and scarring, but there was still considerable viable tumor throughout the neck, including the lymph nodes. The lungs and liver contained areas of nonirradiated tumor where abortive follicle formation, consistent with a poorly differentiated follicular cancer, was recognized (Fig. 5). Again, the appearance was not typical for anaplastic thyroid cancer, with its giant-cell and spindle-cell forms.

This is admittedly an unusual clinical and pathological presentation for a follicular cancer of the thyroid gland, but this diagnosis seems the most reasonable. The possibility of another site of origin of the tumor, such as the tracheobronchial tree, was excluded by careful examination. Also favoring a primary thyroid cancer was the initial clinical presentation of a diffuse goiter, as well as the post-mortem finding of symmetrical replacement of the thyroid gland.

There is an indisputable correlation between irradiation of the head and neck in infancy or childhood and the later development of a thyroid neoplasm. Hempelmann and his associates⁶ have studied carefully a large group of patients who had received thymic irradiation in infancy. Their latest report, based on a 20-year follow-up study, compares 2872 patients at risk with a control group composed of the patients' nonirradiated siblings, numbering 5055 subjects. There were 24 proved thyroid cancers in the irradiated group but none in the control group. Although these numbers are impressive, it must be kept in mind that the population pool at risk was large, and that the

incidence of the development of clinically evident thyroid cancer was less than 1 per cent.

Irradiation of the head and neck area other than the region of the thymus gland may also be followed by the development of thyroid cancer, as exemplified by this case. Although we have never seen this complication after irradiation of eosinophilic granuloma, we have observed osteogenic sarcoma as a post-irradiation complication of that disease. In considering the role of radiation therapy in the management of 30 cases of histiocytosis Smith et al.⁷ cautioned against the use of a dosage higher than 600 rads and stated that higher doses "could present a potential hazard to the patient in the pediatric age range," but there was no specific mention of neoplasia in that report.

What of the interval of 29 years before the development of a thyroid cancer after irradiation? Such a long interval is not unusual, and in the group of patients who had thymic radiation studied by Hempelmann et al. the latent period was a minimum of five years but extended into the fourth decade after irradiation. The

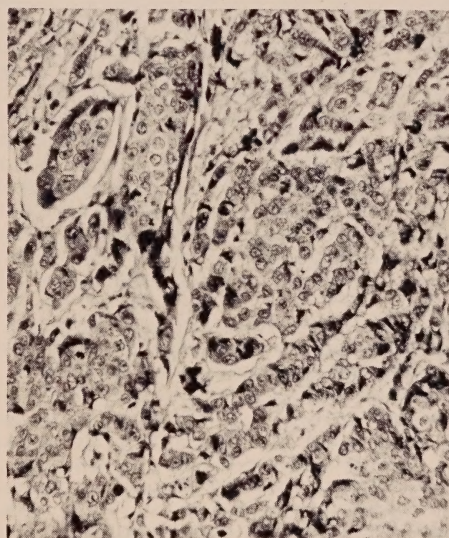


Figure 5. Pulmonary Metastasis, Exemplifying Nonirradiated Thyroid Tumor. (× 200)

data of those investigators suggest that the latent period is inversely proportional to the dose. Another interesting feature of this study is that the incidence curves of both malignant and benign thyroid tumors have risen in the period of 20 to 30 years after radiation.

The most common microscopical forms of thyroid cancer after external radiation are well differentiated papillary and follicular carcinomas, with the great majority having a papillary component. There have

been only isolated reports of undifferentiated or medullary carcinoma.^{3,8,9} However, since undifferentiated thyroid cancer is characteristically a disease of the elderly, its occurrence in younger patients might be expected to be rare. The present case must be considered exceptional and may reflect a transition of a previously well differentiated neoplasm into a poorly differentiated form, a recognized phenomenon in the genesis of anaplastic thyroid cancers.¹⁰

In the current atmosphere of awareness of thyroid cancer complicating radiation therapy it is very important that a distinction be made between thyroid cancers that are clinically evident, as in the present case, and those that are occult or microscopic and are discovered only incidentally during a careful examination of a total-thyroidectomy specimen. Small thyroid papillary cancers are present in a surprisingly large per cent of nonirradiated thyroid glands of adults, ranging from 5.6 to 28 per cent in different population groups.¹¹⁻¹³ Sampson et al.¹¹ have pointed out that the frequency of finding such tumors depends on the thoroughness with which the gland is examined. These small tumors are clinically innocuous,^{14,15} and their inclusion in the statistics on the frequency of thyroid carcinoma provides a distorted concept of radiation-induced thyroid cancers. In the study of Favus et al.,⁴ to which Dr. Levene referred, 60 thyroid cancers were found in 182 operations on irradiated patients who had clinical thyroid abnormalities. Forty-nine (82 per cent) of these carcinomas were occult, ranging in size from microscopic to 15 mm in diameter. Furthermore, 47 per cent of all the thyroid carcinomas in that study were found in patients whose clinically detectable lesion proved to be benign. Extensive operations to remove such small tumors seem unnecessary.

We are fortunate to have with us Dr. Greenberger, who is a resident in radiation therapy at the Joint Center for Radiation Therapy.

DR. JOEL S. GREENBERGER: From 1919 to 1964 more than 200 patients with the diagnosis of eosinophilic granuloma, Hand-Schüller-Christian disease or Letterer-Siwe disease were seen at the Children's Hospital Medical Center. This patient received orthovoltage radiation therapy in two separate courses over a two-year period. In 1946 he received treatment by a 200-kV unit (1.0 mm Al, 0.5 mm Cu) to deliver 600 R in air to each of four fields, including the sphenotemporal region (8 by 10 cm opposed lateral fields) and the mandible (5 by 8 cm opposed lateral fields). This treatment must have produced some scatter radiation to the thyroid gland. In 1947 he received another dose of 300 R in air to an 8-by-8-cm field in the right mastoid region on the same therapy machine. That was the total radiation therapy delivered

to the head and neck. The disappearance of the histiocytosis in this case is consistent with the findings in almost all the cases that we have reviewed in which the patients died of other causes and were examined at autopsy.

A PHYSICIAN: Would the prophylactic use of thyroid hormone be helpful in preventing the development of these tumors? In other words, if a child has received radiation to the thyroid area, would it be wise to put him on thyroid for the rest of his life?

DR. DANIELS: That is a very important question. In every patient whom we see who has received x-ray treatment in childhood we consider thyroid-hormone administration, but we don't know yet if it is effective.

DR. LEVENE: A very important public health problem is involved in this question. There are many thousands of irradiated children in this country, and in some places the possibility that thyroid abnormalities have developed is being investigated.

ANATOMICAL DIAGNOSES

Follicular carcinoma of thyroid gland, poorly differentiated, secondary to remote irradiation (29 years), with widespread metastases to lungs, liver, lymph nodes and bone. (Eosinophilic granuloma, cured).

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SEROTONIN AND MYOCLONIC SEIZURES

MYOCLONUS is a descriptive term for involuntary, brief, jerking movements of a muscle, limb or combination of limbs. It may be symmetrical or focal, rhythmic or irregular and commonly involves the head, face and upper extremities. It characteristically disappears during sleep. Although myoclonus may occur at rest, it is usually precipitated or intensified by movement and emotional or sensory stimuli. It is quite clear that myoclonus occurs in the setting of many dissimilar pathologic states. In the newborn it may be a reflection of severe perinatal brain damage from any cause. In infancy massive myoclonic seizures are often associated with a wildly disordered electroencephalogram (hypsarrhythmia) in the syndrome known as "infantile spasms." They occur as part of the Lennox petit-mal triad and are found in lipid-storage diseases, viral encephalopathies and genetically determined amino acidurias. In adulthood, however, myoclonus is usually encountered as a manifestation of toxic-metabolic encephalopathy, particularly renal failure, and after diffuse anoxic brain damage.¹ This last cause of myoclonic seizures is becoming increasingly more frequent as cardiopulmonary resuscitative techniques are more successful.

The electrophysiologic substrate of these movements, as one might expect, is both varied and clouded. Although many myoclonic jerks are accompanied by synchronous spiking or polyspike-and-wave discharge, this pattern is not uniformly observed, and many myoclonic "seizures" cannot be accurately defined as true epileptic discharge. This situation has given rise to the concept that some, or even most, arise from irritative foci in the lower brainstem or spinal cord, but this idea is difficult to substantiate.

Myoclonic seizures can be produced experimentally by cortical or medial thalamic lesions as well as by a variety of toxic agents, including urea.² Although they may respond to any of the better established anticonvulsants (particularly the benzodiazepines), most patients respond erratically, if at all.

Increasing efforts have been made to delineate biochemical abnormalities for seizure disorders not accompanied by a readily apparent biochemical derangement. Since the synapse between two neurons is one of the most vulnerable sites for the initiation of seizure discharge, neurotransmitters have been particularly suspect. When gamma-aminobutyric acid was identified as a powerful synaptic inhibitor, many investigators attempted to replenish a suspected deficiency in various seizure states, but without success.

The indoleamines have also come under scrutiny. Serotonin (5-hydroxytryptamine, 5-HT) is an important central-nervous-system neurotransmitter with several roles. Particularly, it acts as a central-nervous-system inhibitor. Serotonergic depletion or end-organ blockade leads to hyperactivity and may cause actual seizure discharge. Surgical lesions of serotonergic neurons result in hyperactivity but not overt

seizures. It has been suggested that trimethadione exerts its anticonvulsant effect by elevating brain 5-HT.³ Attempts to treat human seizure disorders with 5-HT, however, have met with mixed results at best.

The dramatic success of neurotransmitter-precursor therapy in Parkinsonism has suggested alternative strategies for therapeutic trials of agents with suppressor or anticonvulsant activity. Whereas most transmitters themselves are not lipid soluble and so cross the blood-brain barrier in very low concentrations, their chemical precursors readily enter the central nervous system. If metabolically capable cells are still present, these precursors can be converted into functional transmitter substances. To aid the clinician further, toxicity, which is mainly a function of the peripheral blood levels of the drug, can be reduced by inhibition of peripheral metabolism, providing an effective central-nervous-system dose at a much lower blood level. This approach, which has been so effective with L-dopa therapy of Parkinsonism, has been used by Van Woert and his co-workers in a clinical study of myoclonus epilepsy reported in this issue of the *Journal*. This study, representing an extension of a recently published work,⁴ uses a serotonin precursor, 5-hydroxytryptophan (5-HTP) and the same peripheral decarboxylase inhibitor (carbidopa) that is so effective with L-dopa therapy. The underlying assumption (no direct proof is yet available) is that 5-HT is deficient or inactive in myoclonic seizures.

The suggestion that 5-HTP might be effective in post-anoxic myoclonic seizures was reported by Lhermitte et al. in an innovative and rather exhaustive pharmacologic study of a single patient.⁵ This premise is supported by Van Woert's data, showing the return to normal of depressed pretreatment levels of cerebrospinal-fluid indole metabolites, at the same time that clinical improvement was observed. Although the clinical variables were controlled somewhat less than one would like, it appears reasonably certain that at least some patients benefited. Van Woert and his collaborators observed that 5-HTP was effective in several types of myoclonus. This observation, if true, suggests a unitary biochemical basis for a group of pathologically quite dissimilar conditions. Alternately, one might propose that 5-HTP has generalized anticonvulsant activity, which is unlikely. In fact, the authors' data suggest that possibly the anoxic group did better. A recent study⁶ has indeed concluded that post-anoxic myoclonus is suppressed by 5-HTP but that other types are not.

As has been observed with central neurotransmitter therapy and psychoactive drugs in general, one must be prepared for conflicting results and seemingly contradictory drug action. For example, after serotonergic neurons are pharmacologically damaged by 5,7-dihydroxytryptamine, 5-HTP initiates myoclonic seizure activity in rats.⁷ Also, seizures induced by topical aluminum hydroxide are associated with increased brain 5-HTP levels.⁸

Regardless of the vagaries of the mode of action of

these drugs, it is clear that transmitter-precursor therapy is an important and effective research strategy and should be vigorously pursued.

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ON DECISION MAKING SURROUNDING DRUG THERAPY: A CONTINUING DILEMMA

A TIME must exist when an established drug proposed for a new treatment is experimental and requires all the apparatus of informed consent, protocols and restricted availability; at some time later the drug enjoys the approbation of common use, accepted or even highly recommended for a stated condition. When, how, and with whose permission does this translation from experimental to standard therapy occur? The answers are not clear.

The physician can be guilty of the sin of commission by premature use of a drug when long-term sequelae may not be known, or equally guilty of the sin of omission if years later the drug is established as efficacious and a patient had been deprived of it some years before.

These issues of timing of acceptance of a form of therapy loom large when lawsuits are related to events some years past, for we do not, and perhaps cannot, clearly document the time of translation from experimental to standard, nor have we a mechanism for making that determination, particularly about an old drug for a new purpose.

The problem comes into focus for the administration of glucocorticoids to women threatened with premature delivery in the presence of evidence of fetal-lung immaturity. Glucocorticoids have been used for a variety of maternal indications in pregnancy for many years without evidence of documented injury to the infant. However, they have not been used systematically

at 28 to 34 weeks in the management of pregnancies that are destined to end in premature delivery, and the results of which have been followed prospectively, carefully and with suitable controls for many years to rule out late unexpected adverse events.

The benefit to the fetus from prevention of hyaline-membrane disease after prenatal acceleration of lung maturity by glucocorticoids is considered by many to outweigh any immediate potential risk from use of the drug.¹ Others await the results of still more controlled trials and follow-up studies now being sponsored by the National Heart, Lung and Blood Institute.

When will such data be sufficient? Who decides? When is it still "experimental" to use glucocorticoids for this purpose, and when is it malpractice to withhold them? How medical minds are to be made up on such an issue is a question not likely to be answered soon. Meanwhile, do we rely on our local expert obstetrician or pediatrician for advice, or do we look for an editorial by an "expert" who says yes or no to an established drug for a new use (such as indomethacin for patent ductus arteriosus)? The *New England Journal of Medicine* appears to solicit such editorials, but has no objective way of knowing their impact on practice.² If, as one senses, the impact is considerable, the burden of responsibility on both the writer of the editorial and the editor is very great indeed. At least in some cases the responsibility for certain forms of therapy can be shared by ad hoc task-force committees of our professional organizations or the FDA, whose recommendations have wide impact, as with the warning of toxicity of hexachlorophene-containing soaps in premature infants.³ Such recommendations often require several years of investigation and study, in a society where current research findings are reported in a much shorter time frame at professional meetings and in publications.

The therapeutic conundrum also works in reverse. When is it appropriate to stop using a therapeutic drug or modality? Despite evidence of the harmful effects of a drug there may be an inordinate delay before physicians change their practice. One example is the use of oxytocin by the intramuscular or buccal route during labor. For nearly a decade this drug, when used in a manner that cannot be carefully titrated against uterine response, has been shown to be potentially harmful to the fetus. Induction of labor or enhancement of desultory labor with oxytocin should require a carefully controlled intravenous dose administered by infusion pump along with careful monitoring of uterine contractions and fetal heart rate. Such a recommendation has been "encouraged" by the American College of Obstetricians and Gynecologists, and this organization "discourages" the use of oxytocin by other methods.⁴ Despite these recommendations many physicians continue to administer oxytocin by the buccal or intramuscular route, with occasional devastating results in the unborn infant.

The lack of a quickly responsive formal mechanism

for asserting the propriety of use of an old drug for a new purpose, or restricting use of an outmoded therapy, promotes of necessity a particularly gray time zone, during which it is difficult to be accused of wrongdoing regardless of the action. It is the lack of boundaries of this twilight zone that produces anxieties for both investigator and therapist.

Attempts to lessen the uncertainty of the twilight zone might be unrewarding or even dangerous. A system that responds quickly to each new report of efficacy would endorse some drugs prematurely; a body of experts could come to a popular but misguided conclusion; a federal agency might be too conservative or slow to respond. The weight of informed opinion, through scientific presentation in publication, eventually influences practice. Unlike the legal process, in which yes-no answers are sought, the practice of medicine is more complex; a yes-no answer is often impossible to give. We hope the courts appreciate this necessary state of affairs and allow due time for establishment of accepted practice.

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THE ROLE OF THE PHYSICIAN AS A PATIENT ADVOCATE*

In Western civilization the physician has assumed many roles. At present, these roles are being critically re-examined. The purpose of this paper is to identify the functions for which the physician is indispensable. Such an identification could have great importance for medical education.

In spite of medicine's obvious involvement with a broad array of social and health issues, the physician's unique contribution lies in the care of the sick. In identifying the care of the patient as the role for which the physician is indispensable, the physician's role in clinical research and education is not being ignored. Indeed, it is possible to assert the unifying notion that in all the many obligations, functions and respon-

*Adapted from a talk given at the Totts Gap Colloquium on "The Limits of Medicine: The doctor's job in the coming era" to be published by Plenum Press, New York.

sibilities that medicine has to society, it is only in the care of the patient that the physician is indispensable. The physician's indispensability in the care of the patient exists, moreover, only as a decision maker. Furthermore, in this decision-making function, the indispensable nature of the role of the physician exists only when decisions are made in the face of uncertainty. Uncertainty is defined here as making decisions without adequate information. When there is no uncertainty, the decision can be more reliably made by a computer. But even decision making in the presence of uncertainty does not require the physician. If one wishes to adopt a completely probabilistic approach, such decisions can also be made more reliably by a computer. The indispensability of the physician in decision making in the presence of uncertainty lies in his role as a patient advocate.

In this role of patient advocate, the physician's cause is his patient's welfare as perceived by the patient and not the promotion of a particular intervention. To discharge this responsibility the doctor must make assessments that are based on his appreciation of the changing interactions between the patient, his environment and his disease. A physician who is 90 per cent "certain" about any decision will always seek additional information in the hope that it will increase the "confidence" with which he makes such a decision. The decision, however, will be either correct or incorrect, and the outcome is independent of the confidence with which the decision is reached. When additional information cannot possibly alter the decision, but only gives rise to a greater sense of comfort on the part of the physician, such additional information is of no benefit to the patient. Its only benefit is in reducing the discomfort of the physician. An enormous amount of information is sought at considerable cost, not for the patient's benefit, but rather for the physician's comfort. It is the physician's job to make decisions in situations that are uncomfortable. Thus, the indispensable role of the physician is that of decision maker, as the patient advocate, when such decisions are uncomfortable because of their uncertainty.

Pellegrino* refers to the management of the process of assessment as the practical domain of the physician. Assessment is the critical activity required to make decisions in the presence of uncertainty. So, above all, the education of the physician should be directed to the acquisition of the knowledge and skills required for assessment and for the role of the patient advocate. The formal education of the potential physician is not now geared to yield such a product. One might postulate that this patient-advocate role would be better served by a return to a more classical and humanistically oriented premedical education. Hu-

manistic concepts are essential to effective decision making that has as its objective the patient's welfare as appreciated by the patient. Furthermore, such a premedical education would certainly increase the likelihood of literacy among physicians. That result alone would justify the investment. However desirable a return to the classics may be, it is unlikely to be decisive because the roots for the development of this type of physician are put down far earlier in one's education, growth and development. Moreover, these humanistic characteristics must be developed in spite of the prevailing standards of society — namely, an exaggerated acquisitiveness, a materialist interpretation of success and a complacency with mediocrity. As a matter of fact, if mediocre care of the patient is all that is sought, the physician is dispensable.

Experience indicates that many physicians possess the critical elements for assuming the decision-making role of patient advocate. If research could lead to an effective early identification of such people, the current selection process for medical school could be modified to increase the likelihood of their admission. Until then, it is unlikely that the selection process will make a meaningful contribution toward the product that we seek. This being the case, medical education must nourish and develop the native potential of its students. The primary concerns of undergraduate medical education must be the provision of the knowledge and skills required for decision making, the furnishing of appropriate role models and the creation of an environment conducive to inquiry.

Whether it has been through altruism, avarice or ignorance, the medical schools' capitulation to unreasonable increases in their enrollments, to excessive commitments to service and to a whole series of extensions justified by social imperatives places in jeopardy that fundamental and most important attribute, the maintenance of an environment that encourages inquiry. Most threatening of all is a capitulation to the social imperative. This pressure from society imposes upon us a tyranny of conformity that destroys the environment that fosters controversy, welcomes iconoclasm, and provides a refuge and a forum for the rebel. The preservation of such an environment is truly indispensable to the proper functioning of medical schools; without it inquiry is stifled, and the critical assessment of data is replaced by dogma. The assessment of data is a research discipline. No medical school has established as primary educational objectives the learning of research, scientific inquiry and the assessment of data. Medical schools do not intentionally or specifically educate or provide an environment for learning such a discipline. Research, if taught at all, is taught by the apprentice method. One result is that few graduates are competent to assess data. But an even more deleterious result is that medical students become accustomed to the acceptance of interpretation of data as a matter of dogma.

*Pellegrino ED: Internal medicine and the functions of the generalist: some notes on a new synergy. *Clin Res* 24:252-257, 1976

for active nephritis that had been collected by the patient's fifth hospital day, the low and decreasing level of renal function represented a major diagnostic and therapeutic problem. After aspirin (4.8 g per day) was stopped and low-dose alternate-day, with later higher-dose daily, prednisone was given, two phases in the increase in creatinine clearance became evident. The early and major improvement, from a clearance of 35 to 79 ml per minute, resulted from the withdrawal of aspirin (Fig. 2). Prednisone administration appeared to be responsible for the increase in creatinine clearance from 79 to 96 ml per minute.

Group Analysis

The response of renal function to therapeutic doses of aspirin in 45 patients and three normal volunteers, prospectively evaluated, was analyzed for frequency and possible predisposing factors. Among these 48 subjects, 19 were reactors (Fig. 3), with increases in serum creatinine ranging from 27 to 163 per cent and in blood urea nitrogen from 42 to 270 per cent (Fig. 4). Sequential creatinine-clearance data, available in 11 of the 13 reactors with systemic lupus erythematosus, revealed corresponding decreases in creatinine clearance of as much as 58 per cent (Fig. 4). Revers-

bility of these effects was demonstrated in all nine of the patients in whom such data were collected. Among the subjects who did not meet the criterion as a reactor, small or inconsistent changes in serum creatinine and blood urea nitrogen were often seen but could not be reliably distinguished from variation due to laboratory error.

The reactors were compared to the others in terms of age, sex, prevalence of hypertension and medications taken. No statistically significant differences were noted, and aspirin was the only apparent cause for the changes in laboratory findings.

Thirteen of 23 patients with systemic lupus erythematosus, four of 22 with rheumatoid arthritis and two of three normal volunteers demonstrated aspirin-induced alterations in renal function. The prevalence of reactors in systemic lupus was significantly higher than that in rheumatoid arthritis ($P = 0.007$); a meaningful prevalence could not be established for the normal volunteers. Because of the higher rate in systemic lupus, we sought possible predisposing factors in the patients with that disorder. The occurrence of aspirin-induced change in serum creatinine was related to the presence of active nephritis ($P = 0.035$) or low serum C3 ($P =$

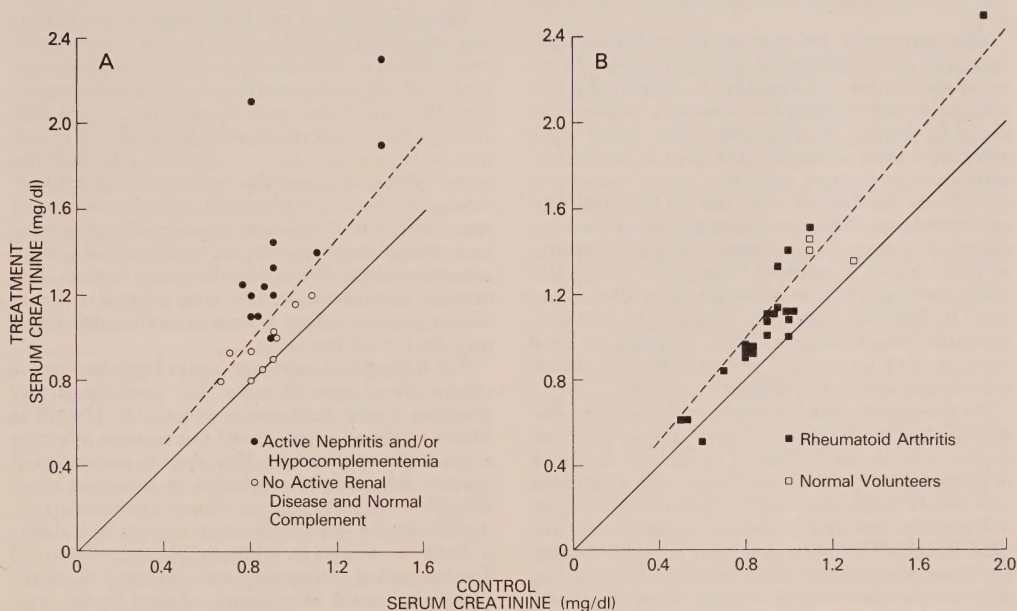


Figure 3. Changes in Serum Creatinine during Aspirin Administration.

Serum creatinine concentrations before and during aspirin therapy in all patients with systemic lupus erythematosus (A) and in patients with rheumatoid arthritis and normal volunteers (B) are shown. The solid diagonal represents the line of identity between control and treatment values of serum creatinine, and the dashed diagonal the minimum change necessary to qualify as a reactor (cf. Data Analysis section). All patients falling above the dashed line were classified as reactors. In A, closed circles represent patients with active nephritis or low serum C3 (or both), and open circles those with quiescent or no clinically evident renal disease and normal complement. In B patients with rheumatoid arthritis are designated by closed squares, and normal volunteers by open squares.

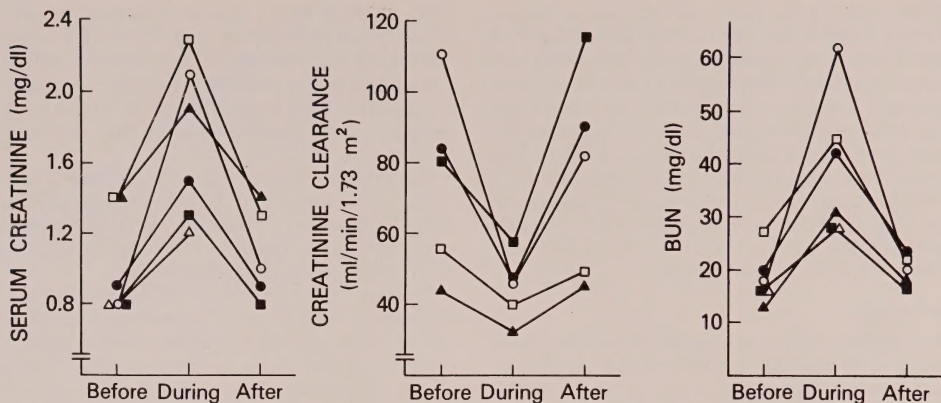


Figure 4. Changes in Renal-Function Measurements in Patients with Systemic Lupus Erythematosus during Aspirin Administration.

Six of 13 reactors are shown in detail. Each symbol denotes an individual patient. In all patients except the one designated with the open triangle the reversibility of the aspirin-induced effects was documented. For the sake of clarity, the other seven reactors are not included.

0.030). Initial creatinine clearance did not correlate with such changes, nor did anti-DNA antibody levels.

Although either active nephritis or hypocomplementemia alone produced statistically significant associations, neither could account for all patients. The concept of "active nephritis," however, is difficult to define by urinary measurements alone. Since lupus nephritis is often associated with low C3, the relation between renal changes and either active nephritis or low C3 was investigated. Only one of 13 patients with aspirin-induced changes was neither "active" nor hypocomplementemic; that patient had had documented renal disease, considered "quiescent" during this study, and had a C3 just above the lower limit of normal. In addition, only one "active," hypocomplementemic patient failed to show a change in renal function with salicylates; this was the one patient whose renal status was difficult to classify.

Because aspirin-induced hepatitis occurs more frequently in systemic lupus erythematosus than in rheumatoid arthritis and because it appears to be related to general activity of disease,¹⁸ a possible association with renal changes was sought. Patients with systemic lupus who had aspirin-induced hepatitis were distributed equally between those showing renal changes and those who did not. Only one of the four reactors with rheumatoid arthritis evidenced an aspirin-induced hepatitis.

Renal function has also been studied in patients with systemic lupus erythematosus receiving other nonsteroidal anti-inflammatory agents. Although our experience is limited, we have observed similar renal changes in two patients with systemic lupus erythematosus receiving indomethacin and in one receiving naproxen.

DISCUSSION

The occurrence of striking changes in renal function concomitant with therapeutic doses of aspirin in some patients with systemic lupus erythematosus prompted a detailed analysis of our patient population. We have found such changes in patients with systemic lupus and rheumatoid arthritis and in normal volunteers, but they were significantly more frequent in systemic lupus than in rheumatoid arthritis. Among patients with systemic lupus, the presence of active nephritis or hypocomplementemia appeared to be a predisposing factor for the occurrence of aspirin-induced changes. We believe that these findings indicate that renal function ought to be assessed with caution in patients taking aspirin or similar drugs that may alter renal function.

The influence of aspirin on the kidneys has been of interest for at least 60 years. The transient urinary shedding of cells and casts investigated by Hanzlik in 1916^{3,4} has been quantitated^{5,6} but remains a finding of uncertain implications. The possible association of aspirin with analgesic nephropathy continues unresolved^{10,11} although patients with rheumatoid arthritis, who have a large exposure to aspirin, have slightly lower than average values for serum creatinine.²³ The continuing controversy² over the effect of aspirin on salt and water metabolism, initiated by the demonstration in the early 1900's of "salicyl edema" and decreased urinary flow,¹ has been amplified by more recent demonstrations of specific interactions between aspirin and the mineralocorticoid system. Aspirin, which antagonizes the diuretic effect of spironolactone,^{24,25} can bind competitively with aldosterone and spironolactone in isolated kidney slices.²⁶ Additional attention has been called to the ability of

aspirin to inhibit prostaglandin synthesis¹²⁻¹⁴ and to the possible role of such inhibition in the modulation of sodium excretion and renal blood flow.^{15,16}

Clinical experience with salicylate-renal interactions has been variable. Hanzlik, in 1917, found that extremely large doses of salicylate increased blood urea nitrogen and decreased phenolsulfonphthalein excretion in some but not all patients.^{3,4} Inconsistent decrements in glomerular filtration rate have been reported in clinical studies employing single oral doses of aspirin⁷ or intravenous infusions of acetylsalicylate.⁸ Others, however, have failed to demonstrate any acute changes in inulin clearance but have shown effects on the renal tubular handling of sodium and water.⁹ In a study more comparable to the therapeutic situation in inflammatory diseases, aspirin was given by mouth for as long as 10 days, and glomerular filtration rate, measured by ⁵¹Cr-EDTA clearance, was not significantly changed.²⁷ Variable changes in serum creatinine and creatinine clearance have been described.^{8,18,28}

The relatively high rate and large magnitude of an aspirin-induced effect on renal function in our patients may have been due to several factors. Most previous studies have involved the acute administration of aspirin rather than more prolonged therapy; our data (Fig. 1 and 2) suggest that this effect may take several days to develop fully. Furthermore, patients with systemic lupus erythematosus appear to be more likely to demonstrate such changes. Our data suggest that this observation is related to the presence of active nephritis, a condition in which prostaglandins may have an important role.^{29,30}

Several questions remain unanswered by our data. Changes in renal function occurred with salicylate levels of 20 to 25 mg per deciliter although in some patients higher levels occurred. Precise dose-response relations could not be established although patients having no changes with salicylate levels of 10 mg per deciliter demonstrated increased blood urea nitrogen and serum creatinine at levels of at least 20 mg per deciliter. Similarly, the maintenance of changes in renal function with continuation of aspirin, although observed for as long as two to three weeks, was not studied for longer periods. Attenuation of the effect was not observed during inpatient study, and outpatient salicylate levels were too variable to allow for any conclusions to be drawn. No patient has shown a progressive decline in renal function beyond the initial decrement with continued use of aspirin.

We have also observed a change in renal function in one patient with systemic lupus erythematosus given naproxen and in two given indomethacin. Indomethacin has been associated with decreased creatinine clearance in patients with Bartter's syndrome³¹ and with elevated serum creatinine in certain infants.^{32,33} Fenoprofen has caused elevated blood urea nitrogen in some patients with rheumatoid arthritis.³⁴ Despite their structural dissimilarities, one common feature of these drugs is their ability to inhibit prostaglandin

synthesis.^{12,35-37} If this inhibition, with a concomitant change in renal blood flow, were the mechanism for the alterations in renal function, one might expect the changes reported above to be common to all the non-steroidal anti-inflammatory agents that inhibit prostaglandin synthesis. Awareness of the potential for aspirin, and other medications, to alter renal function in clinical situations in which it may influence management decisions is critical for proper diagnostic evaluation and therapeutic intervention.

We are indebted to Dr. John L. Decker for reviewing the manuscript.

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SPECIAL ARTICLE

TELEVISION VIOLENCE — REACTIONS FROM PHYSICIANS, ADVERTISERS AND THE NETWORKS

MURRAY FEINGOLD, M.D., AND G. TIMOTHY JOHNSON, M.D.

Abstract In response to our call for letters on television violence we received more than 1500 letters from readers of the *Journal*. Seventy-two per cent of the leading television advertisers responded to a subsequent letter requesting a description of their policies regarding content of the programs they sponsor. Their responses included exculpatory factors such as lack of control over programming, the limited amount of available advertising time and censorship.

We presented these responses to network repre-

sentatives. They commented on the difficulty in defining violence, the current decrease in the amount of violence shown and their activities in response to this issue.

We maintain that the burden of proof that television violence does no harm lies with those who introduce it into society. Advertisers and networks will respond, we believe, to the problem of television violence if continuous public pressure is maintained. (*N Engl J Med* 296:424-427, 1977)

THE April 8, 1976 issue of the *Journal* included an article by Somers entitled "Violence, Television and the Health of American Youth." It prompted an editorial comment concluding with this boldly stated "call to arms" to the medical profession: "Or shall we medicos and our spouses and friends sit back, as we have been doing, and fold our hands over contented bellies, while the after-dinner entertainment of our children shows that nothing can be accomplished in this world without brass knucks, kicks in the groin, switch blades or Saturday Night Specials."¹

As physicians who are also television medical editors we felt a sense of responsibility to respond to this admonition. We did so by calling for letters of concern from the readers of the *Journal* and promising to convey that expression to appropriate decision makers.² This report summarizes our experiences.

Readers' Response

We received over 1500 letters from physicians and others in response to our call for letters. The majority

of the letters came from pediatricians and psychiatrists, but all specialties were represented. Many writers presented anecdotal information concerning the deleterious effects that violence had had on their patients and family members. Some related that they were so angered by the amount of violence being portrayed on television that they no longer had a television set in their homes.

Contact with Advertisers

Armed with this response, we took a second step by writing the following letter to the 100 leading national television advertisers as identified in the trade journal *Advertising Age* (if the reader is interested in an up-to-date listing of the leading national advertisers, the address of *Advertising Age* is 740 Rush Street, Chicago, IL 60611):

A recent issue of the widely read and influential *New England Journal of Medicine* contained an article and editorial (copies enclosed) concerning the problem of violence on television. As physicians who serve as medical editors of two Boston [affiliated] network stations (ABC and NBC), we were moved to extend the response to this problem by inviting letters from the readers of the *NEJM*.

The response was dramatic — now over 1000 physicians from all over the country. Many of the writers were pediatricians who

From the Department of Pediatrics, Tufts University School of Medicine, and the Department of Continuing Education, Harvard Medical School (address reprint requests to Dr. Feingold at New England Medical Center, 171 Harrison Avenue, Boston, MA 02111).

described personal experiences with the effects of TV violence on their young patients. Many physicians wrote both as professionals and concerned parents. We found the reading of these letters to be one of the most stirring experiences of our lives.

It is our personal conviction — and that of a significant number of our colleagues in medicine — that the pervasive portrayal of violence on TV has a destructive influence in our society. While we cannot prove this conviction in a traditionally scientific manner, we can suggest that the burden of proof lies in the opposite direction — i.e., those who support such programming have the burden to prove that it does no significant harm. More positively, we would suggest that the time has come for all of us — professionals, concerned parents and interested citizens — to trust our instincts and common sense and *do* something before the battle is lost.

We are asking you — as the head of one of the companies identified as a leading TV advertiser — to join us in this concern. Specifically, we are interested in your policies concerning the content of the programs you sponsor. Do you intend to sponsor programs clearly identified as “violent?”

We plan to include your response as part of a promised report to our colleagues to be published in an upcoming issue of the *NEJM* and simultaneously released to the press.

The responses that we received (72 per cent to date) were thoughtful and provocative.* Though the range of thought and emotion expressed varied, certain themes were repetitive. The most prominent of these themes claimed “lack of control” over program content. Such a “Catch-22” situation was described by McDonald’s Corporation vice-president for public affairs:

Our marketing vice-president has already visited all three major networks and strongly expressed our concern and dissatisfaction with the inventory of suitable programming which meet our criteria. However, the networks argue that they are providing what the public wants. They claim that the ratings of these shows are high, and are necessary to compete for the sale of advertising. The agencies claim that they must purchase the most cost effective shows for their clients. The advertisers claim that the inventory for their selection is limited and that they have no choice but to buy commercial messages on available programming.

One of the technical problems continually mentioned by the companies is the difficulty of exerting control over so-called “spot” or “scatter” advertising — i.e., the practice of buying advertising space months or even years ahead of time without knowing the actual program in which it will appear. The vice-president for advertising for Johnson and Johnson wrote, “Think of it. We don’t know the exact title of the movie we bought; we don’t know the exact content of the new programs; we don’t know which ‘best seller’ will be developed as a T.V. show, and yet we — the advertiser — we bought it all!” However, some companies described efforts to monitor the wide range of programming in which their pre-bought advertisements ultimately appeared.

Other companies expressed frustration over the limited amount of available advertising and suggested that a fourth network is needed to allow more com-

petition. As the director of marketing management for the Joseph Schlitz Brewing Company wrote, “The shortage of network television air time which sponsors can purchase has made this very much a sellers market; and this again restricts the influence of the advertisers.”

Another recurring theme was the concern about “censorship” if advertisers attempted to exert “influence.” Some companies thought that the television networks were already very sensitive and responsive to public opinion. Others expressed confidence in the ability of the average American to “tune in” or “tune out” appropriately. The advertising manager for Volkswagen stated, “We should rejoice in the freedom we enjoy in this country of being able to view, read, listen, etc., to any work of our choice, and furthermore to ignore or shut out any particular work we reject.” Others were less optimistic about the possibilities for many — especially children — to exert self-control. As the president of Miles Laboratories wrote, “What appears on television can really only be censored by the household *after* the fact, and whatever damage may have been done cannot be either defined or erased.” The Ford Motor Company representatives made a careful distinction between advertisers’ power to withdraw advertising from programs they consider objectionable — a practice that they support — and attempts to exert prior control over content — a pressure that they do not exert.

Overall, the responses from the advertisers were encouraging. The vast majority expressed genuine concern that something must be done, even while acknowledging the difficulties involved. Most of the companies sent policy statements already in effect, suggesting that they have given thought to solving the problem of “excessive” and “gratuitous” violence on television.

CONTACT WITH NETWORKS

On Friday, September 24, 1976, we met in New York City in three separate meetings with representatives of the three major networks.* At each meeting we presented the responses of the *Journal* readers and raised our own concern about violence on television. All three networks stated that they were aware of the issue and were reacting to it. However, they continually stressed the difficulty of reducing a complex issue such as violence to a simple definition. Nonetheless, in published material the networks have “working” definitions of violence. For example, in the CBS “Network Primetime Violence Tabulation for the

*We subsequently discovered that our letter also prompted considerable discussion at the network level. Some of the advertisers — either directly or through their agencies — expressed concern to the networks about “the Feingold-Johnson letter.”

*Robert Kasmire, vice-president for corporate affairs, NBC; J. Ronald Milavsky, Ph.D., director of social research, NBC; William Rubens, vice-president, research and corporate planning, NBC; Arthur Taylor, then president of CBS; E. Kidder Meade, vice-president for corporate affairs, CBS; David M. Blank, Ph.D., vice-president and chief economist, CBS; Gene P. Mater, vice-president and assistant to the president, CBS/Broadcast Group; Alfred R. Schneider, vice-president in charge of broadcast standards and practices, ABC; Richard P. Gitter, director, East Coast Department of Broadcast Standards and Practices, ABC; and their psychiatric and educational consultants.

1975-1976 Season," violence was defined as "the use of physical force against persons or animals, or the articulated, explicit threat of physical force to compel particular behavior on the part of a person." It further interpreted that definition to include "all acts *intended* to cause physical harm (for example, attempted murder)...whether they were successful or not.... Unintentional injuries (such as might result from a shove merely intended to get someone out of one's way) were not considered violent, nor were threats that were not backed up by a show of force (along the lines of 'I'll get you someday')."

The networks stressed their involvement in a variety of studies concerning television violence. They also emphasized the existence of a "standards division" that reviews program content to be certain that it conforms to company and industry standards. At ABC, Alfred R. Schneider, who is in charge of the Standards and Practices Department, reports to the president of the parent company and not to the president of the television division. He states that the reason for this setup is that "program and commercial acceptability should never have anything to do with the question of sales and profits. In appearance and in reality, they must be totally independent of each other." NBC and CBS, although structured differently, also claim that their "standards divisions" function independently of the sales and program departments.

During our meetings, the network representatives indicated their particular concern with the content of children's programs. They described a process of review at all stages of preparation, not only by network representatives, but also by various paid consultants, including psychiatrists, psychologists, educators and social scientists. However, they also stressed the point that they consider the parent primarily responsible for a child's television viewing habits. As ABC's Schneider says,

If there are adverse effects of what television does, it stands to reason that those effects will be greatest on the most vulnerable members of our society, our children. We recognize this responsibility, but we also recognize that this is to be a shared obligation. There is no substitute for discriminatory parental supervision. While we must exercise a great deal of care with respect to what children watch, we must also remember that we serve a total audience, and to do so we must maintain television as a vigorous, vital and changing medium.

The networks presented data substantiating their claim that the amount of violence now shown on television has been reduced from that of previous years. We later approached Donald McGannon, president of Westinghouse Broadcasting Company, who is still concerned:

[because] in recent years over fifty percent of primetime programming has content that is based on violence, crime and adult material. This was not changed by the "family viewing" hour, which was a "charade" and simply loaded such content into the nine to eleven evening period and completely eliminated any choice. On examination, one would find that the plot does not require the quantum of violence, etc., but this is included in order to develop a stronger share of audience and demographic characteristics of retail buyers. The inability to establish a direct

causal relationship between television violence and subsequent viewer behavior should not be a pre-condition for corrective action. Television is the most powerful social force in our society and must be programmed with great sensitivity, care and caution.

The network representatives expressed strong disagreement with two articles on the subject of television violence that have recently appeared in the medical literature. John A. Schneider, president of CBS Broadcast Group, has stated that the article by Rothenberg³ "has presented a misleading report on the effects of television violence on children and youth. Rothenberg's article is filled with so many factual errors and serious over-simplifications...and mis-statements...of scientific conclusion that we initially ignored his article." William Rubens, vice-president for research and corporate planning at NBC, has commented that "the article on 'Violence, Television and the Health of American Youth' by Somers, which also prompted an editorial endorsing its views, contains significant distortions as well as various errors of fact indicative of a casual and popularized approach to the data."⁴

After our meeting with the network representatives we met in Boston with Peggy Charren and Deborah First, president and executive director of Action for Children's Television (ACT). We discussed our experiences with the networks and requested their comments concerning violence on television. They sent us the following statement:

Action for Children's Television has always believed that the rush for ratings holds the real answer to the question of why violence has a place of such prominence on the broadcaster's schedule. Programs peppered with fast action or violence seem to attract considerable audiences, and can therefore command a higher price tag per minute from sponsors who are eager to peddle their wares to vulnerable young consumers. Prodded by recent vociferous protests from the medical profession and the threat of a consumer boycott of products promoted on excessively violent programs, however, many advertising agencies have now joined the ever-growing citizen army which is determined to stem the daily invasion of media brutality into their homes.

A realistic appraisal of television's influence on the lives of this country's young people requires thoughtful but unyielding action by ACT and other similarly-minded adult advocates. As caretakers of the next generation, all concerned citizens must pose some of the questions that the broadcasting industry is reluctant even to ask. It is ACT's conviction that the problems with children's television viewing are not merely that the numbers of violent incidents per hour are so many, but that the opportunities to select something different are so few.

PERSONAL OBSERVATIONS

The effect of television violence on the viewer is an emotionally charged issue that is further confused by the fact that the data now available are conflicting. The readers of the *Journal* who wrote to us were convinced that violence on television can adversely affect the viewer, especially children. These views were not based on scientific data but on "clinical impressions" and "common sense." The network point of view is that most physicians know very little about the data currently available. We question, given the lack of hard data, whether the diverse opinion of experts is of

any greater value than clinical impressions. Although recognizing the lack of definitive data, we believe there is an inconsistency in the networks' attitude, which questions the effect of television violence while championing the impact of television advertising.

Our basic premise in approaching the networks was — and is — that the burden of proof that violence on television does no real harm lies with those who introduce such a potent force into the societal brew. We obviously reflect the current responsibility placed on the medical profession when it is introducing new modes of therapy. Some of the network representatives found this approach to a social issue unfamiliar and irritating. They instead reflected the approach of criminal law, which insists that innocence exists until proof to the contrary is established.

Although we were impressed with the concern and effort currently expended by the networks in evaluating the impact of television violence, we also believe that profit is one of the most important factors, if not

the most important, in determining program policy. Therefore, public pressure that would have an effect on advertising and network pocketbooks, directly as in boycott movements, or indirectly in terms of concern for image, seems to offer the most effective way to influence program content. We believe that both the sponsors and the networks are currently sensitive to the "violence problem," and will be responsive to intelligent efforts directed to their consciences and cofers. However, we also believe that continuing public pressure is absolutely essential in maintaining such responsiveness.

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MEDICAL PROGRESS

NONINVASIVE CARDIAC DIAGNOSIS (Third of Three Parts)

ALFRED F. PARISI, M.D., DONALD E. TOW, M.D., W. ROBERT FELIX, JR., M.D.,
AND ARTHUR A. SASAHARA, M.D.

ASSESSMENT OF VENTRICULAR FUNCTION

A number of noninvasive technics have been advocated as reflecting left ventricular performance. These methods include systolic-time intervals, echocardiography and imaging of the left ventricular chamber with radionuclides during systole and diastole.

The determination of systolic-time intervals is noninvasive, extremely rapid and simple.^{106,107} A long pre-ejection period with an accompanying short left ventricular ejection time is typically associated with a low ejection fraction and heart failure. In some circumstances, such as edematous states, the intervals have proved helpful in distinguishing the heart failure of cardiomyopathy from constrictive pericarditis.¹⁰⁸ The latter condition is usually associated with normal systolic-time intervals.

Systolic-time intervals, however, have not achieved widespread popularity for the assessment of ventricular function. The technic has been extensively evaluated in patients with acute myocardial infarctions¹⁰⁹⁻¹¹¹ with the expectation of predicting clinical deterioration — particularly severe heart failure and shock — in this setting. In patients with acute infarction, however, the hemodynamic variables upon

which the pre-ejection period and left ventricular ejection time depend can rapidly change in opposite directions in a manner that offsets the ability of the intervals to relate to any single hemodynamic measurement. The net result is that systolic-time intervals, taken by themselves, are not useful in managing or predicting the outcome of patients with acute myocardial infarction. In addition, since the 1968 study of Garrard, Weissler and Dodge, there has been little confirmation of the diagnostic accuracy of systolic-time intervals for predicting ventricular function in large groups of patients with chronic coronary disease.¹¹² The technic also is further limited by its dependence on normal intraventricular conduction as well as normal sinus rhythm.¹¹³

Several studies have shown echocardiographic measurements to correlate with ventricular volumes and ejection fraction.¹¹⁴⁻¹¹⁶ However, this approach in predicting ventricular function in individual patients, derived from approximately transverse diastolic and systolic measurements of the left ventricle, has been open to criticism.¹¹⁷ In particular, coronary-artery disease often involves localized disorders of left ventricular contraction that can alter systolic chamber dimensions in either direction, depending on whether or not a hypocontractile or hypercontractile area of the ventricle is traversed by the echocardiographic beam. As a result the correlation of echocardiographic and angiographic ventricular volumes in coronary disease is poor when left ventricular asynergy is present.¹¹⁸

From the departments of Medicine (Cardiology), Nuclear Medicine and Surgery, West Roxbury Veterans Administration and Peter Bent Brigham hospitals and Harvard Medical School (address reprint requests to Dr. Parisi at the Veterans Administration Hospital, 1400 VFW Parkway, West Roxbury, MA 02132).

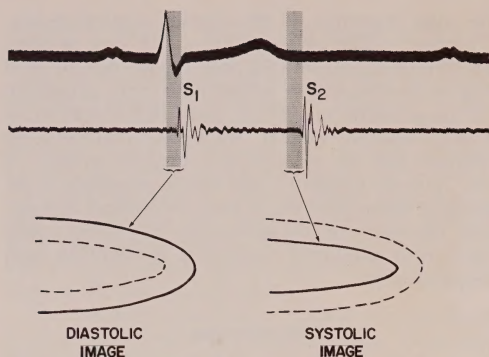


Figure 9. Schematic Illustration of the Technic of Gating. The images of diastole and systole are integrated over several cardiac cycles. As indicated by the shaded bars the electrocardiographic QRS complex is used to time the formation of diastolic images while systolic imaging is accomplished immediately before S_2 .

When abnormalities of anterior or anterolateral wall motion (which are not traversed by the echocardiographic beam) exist, echocardiographic ejection fractions are often overestimated.^{117,120} Despite current limitations, however, the echocardiographic approach has potential for overall rapid noninvasive assessment of left ventricular function. The results of recent studies of Teichholz et al., which accurately predicted ejection fractions by using the B-scan technic, indicate that a fuller image of the left ventricle is likely to have more reliable information than can be obtained by conventional M-mode technics.¹²¹ With the development of multiscan and sector-scan approaches to the left ventricle, echocardiography may

indeed prove to be the most practical, rapid means of assessing left ventricular function in the future.^{122,123}

Radionuclide evaluation of left ventricular function by means of the gamma camera and gating currently appears to be the most reliable noninvasive means of approximating angiographic evaluation of left ventricular performance. Several independent studies have shown correlation coefficients of 0.9 or better when ejection fractions determined by radionuclides are compared to angiographic ejection fractions.¹²⁴⁻¹²⁷ In these studies, images of the left ventricle during systole and during diastole are separately obtained after intravenous injection of a labeled intravascular substance such as ^{99m}Tc albumin. The build-up of the images involves electronic switching of the gamma camera controlled by electrocardiographic or phonocardiographic monitoring of the heartbeat. Thus, radioactivity only during systole or diastole is recorded. This method is commonly known as gating (Fig. 9). The images obtained represent composites of many beats. Ejection fraction is calculated from the systolic and diastolic images by planimetry or computer data processing.

More recently, assessment of left ventricular function by the first radionuclide transit through the heart has been advocated (Fig. 10). This purpose is achieved with a high-speed scintillation camera coupled to a computer system.^{128,129} The resulting images are reported to be superior in both spatial and temporal resolution to those obtained by the gating method.¹³⁰ Insufficient reports are available at present for a critical evaluation of this first-pass approach.

Radionuclide imaging of the left ventricle can also be used to evaluate regional left ventricular function. Abnormally contracting segments can be detected by this means, providing an important clue to the likeli-

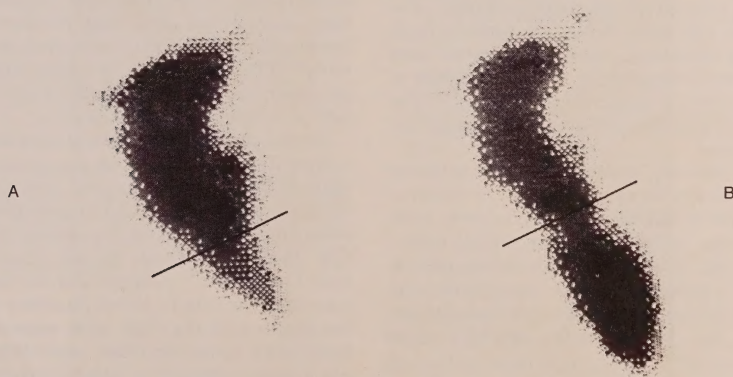
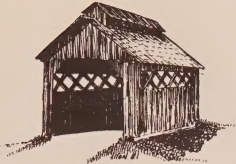


Figure 10. ^{99m}Tc Scintiscans from First Pass of Radionuclide through the Left Ventricle in Left Anterior Oblique View Obtained with a Multicrystal Gamma Camera.

The systolic (left) and diastolic (right) outlines of the left ventricle can be seen below the plane of the aortic valve (solid line).



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GAY RESEARCH QUESTIONNAIRE

This questionnaire attempts to gather information about the feelings, concerns and experiences of gay men. As a gay doctoral student in the field of Clinical Psychology, I have interest in this area of research.

Your name was chosen from a list of men affiliated with a gay organization or through personal contact with a member of such a group. Complete confidentiality is assured.

No in depth study of gay males in the New England area has ever been done. Such a study is long overdue, and can bring to light important issues, such as how gays feel about themselves, how they deal with each other, and how they fit into society. Your cooperation is needed, urged, and appreciated. All responses will be kept anonymous.

Allow yourself at least one hour to complete the questionnaire. Pick a time when you can be free of interruptions. Limit your responses to the specific items on the questionnaire and please answer each item to the best of your ability. Enclosed is a stamped envelope in which you can return your questionnaire.

Thanks for your cooperation,

Bob Torres

Bob Torres

GAY RESEARCH QUESTIONNAIRECONSENT FORM

I understand this questionnaire has been designed to study the feelings, experiences, and concerns of gay men.

I understand the nature of the questionnaire and agree to complete it.

I understand I will not be asked for any further commitment and that all information contained in the questionnaire is strictly confidential.

I understand that my name will not be used in any way, and that codes rather than names will be used to identify responses.

I understand that my participation in this study is voluntary and that I am free to withdraw from it at any time.

I understand that I may address any questions about the study to Robert Torres, Department of Psychology, John Dewey Hall, University of Vermont, Burlington, Vermont, 05401.

I (would / would not) like to receive a copy of this study's results.

Participant's signature

Participant's full name

* IN ORDER TO INSURE ANONYMITY, THIS FORM MAY BE DETACHED AND RETURNED SEPARATELY.

Participant's age Last grade completed Participant's occupation

BELOW IS A LIST OF STATEMENTS DEALING WITH YOUR GENERAL FEELINGS ABOUT YOURSELF. IF YOU AGREE WITH THE STATEMENT, CIRCLE A. IF YOU STRONGLY AGREE, CIRCLE SA. IF YOU DISAGREE, CIRCLE D. IF YOU STRONGLY DISAGREE, CIRCLE SD.

	1 Strongly Agree	2 Agree	3 Disagree	4 Strongly Disagree
1. On the whole, I am satisfied with myself.	SA	A	D	SD
2. At times I think I am no good at all.	SA	A	D	SD
3. I feel that I have a number of good qualities.	SA	A	D	SD
4. I am able to do things as well as most people.	SA	A	D	SD
5. I feel I do not have much to be proud of.	SA	A	D	SD
6. I certainly feel useless at times.	SA	A	D	SD
7. I feel that I'm a person of worth, at least on an equal plane with others.	SA	A	D	SD
8. I wish I could have more respect for myself.	SA	A	D	SD
9. All in all, I am inclined to feel that I am a failure.	SA	A	D	SD
10. I take a positive attitude toward myself.	SA	A	D	SD

FOR EACH CATEGORY INDICATE HOW YOU EXPERIENCE BEING GAY.

11. Amount of regret over being gay

- 1: None
- 2: Some
- 3: A great deal

12. Do you often worry about having your sexual preference exposed?

- 1: Never worry
- 2: Sometimes worry
- 3: Often worry

13. Amount of satisfaction over being gay.

- 1: None
- 2: Some
- 3: A great deal

14. If there were a magic pill to make you heterosexual would you want it?

- 1: Yes
- 2: No

15. If there were a magic pill to make you more comfortable being gay would you want it?

1:Yes

2:No

16. How long have you been "out", i.e., acknowledged your gayness?

1:to yourself

2:to other gay men

3:to others in general

FOR EACH CATEGORY INDICATE THE EXTENT TO WHICH OTHERS KNOW ABOUT YOUR BEING GAY.

17. Mother

1:Neither knows nor suspects

2:Suspects

3:Knows

18. Father

1:Neither knows nor suspects

2:Suspects

3:Knows

19. Siblings

1:Neither knows nor suspects

2:Suspects

3:Knows

20. Other Relatives

1:None know

2:Few Know

3:Most know

21. Employer

1:Neither knows nor suspects

2:Suspects

3:Knows

22. Fellow Workers

1:None know

2:Few know

3:Most know

23. Heterosexual Friends

1:None know

2:Few know

3:Most know

24. Neighbors

1:None know

2:Few know

3:Most know

FOR EACH CATEGORY CIRCLE THE STATEMENT THAT BEST DESCRIBES YOU.

25. How much time do you spend with friends?

- 1: More with gay friends
- 2: Equal time
- 3: More with non-gay friends

26. How important is it for you to have gay friends?

- 1: Not important
- 2: Somewhat important
- 3: Very important

27. Is there anything you can do to improve the way gays see themselves or the way in which society views gays?

- 1: Not much
- 2: A little
- 3: A lot

Which of the following activities have you participated in?

28. 1: Entered a gay bar (yes/no)
 2: Membership in a gay organization (yes/no)
 3: Marched in a gay parade (yes/no)
 4: Other _____

29. Have you ever had an ongoing relationship with a man? If so, what is the longest time such a relationship has lasted.

- 1: Never have had an ongoing relationship
- 2: Have had an ongoing relationship for _____.

ANSWER EACH STATEMENT TRUE OR FALSE BY CIRCLING T OR F.

- | | | |
|--|---|---|
| 30. I often find social occasions upsetting. | T | F |
| 31. I usually feel calm and comfortable at social occasions. | T | F |
| 32. I try to avoid talking to people unless I know them well. | T | F |
| 33. If the chance comes to meet new people, I often take it. | T | F |
| 34. I am usually nervous with people unless I know them well. | T | F |
| 35. I usually feel relaxed with someone when we meet for the first time. | T | F |
| 36. Being introduced to someone makes me tense and nervous. | T | F |
| 37. I tend to withdraw from people. | T | F |
| 38. I don't mind talking to people at parties or social gatherings. | T | F |
| 39. I find it easy to relax with other people. | T | F |

PLEASE READ EACH STATEMENT CAREFULLY AND DECIDE WHICH RESPONSE BEST FITS OR SUITS YOUR OPINION OF YOURSELF. CIRCLE THE APPROPRIATE NUMBERED RESPONSE PLEASE DO NOT LEAVE ANY STATEMENT BLANK.

	1	2	3	4
	STRONGLY AGREE	AGREE	DISAGREE	STRONGLY DISAGREE
40. I expect other people to be honest and open.	SA	A	D	SD
41. I am less trusting than the average person.	SA	A	D	SD
42. I am more trusting than most of my friends.	SA	A	D	SD
43. I am suspicious of other people's intentions.	SA	A	D	SD
44. I am less trusting than the average gay person.	SA	A	D	SD
45. I have faith in human nature.	SA	A	D	SD
46. I feel that other people can be relied upon to do what they say they will do.	SA	A	D	SD
47. I feel that other people are out to get as much as they can for themselves.	SA	A	D	SD
48. I have faith in the promises or statements of other people.	SA	A	D	SD
49. I am cynical (pessimistic).	SA	A	D	SD

BELOW IS A LIST OF TEN QUESTIONS ASKING FOR PERSONAL INFORMATION ABOUT YOURSELF. INDICATE HOW MUCH INFORMATION ABOUT A PARTICULAR ITEM YOU HAVE REVEALED TO SOMEONE IN YOUR PAST.

- WRITE IN A 1 IF YOU KNOW YOU HAVE NEVER TALKED ABOUT THAT ITEM TO A PERSON.
 WRITE IN A 2 IF YOU HAVE TALKED IN GENERAL TERMS ABOUT THAT ITEM, BUT NOT IN FULL DETAIL. ANOTHER PERSON HAS BEEN GIVEN ONLY A GENERAL IDEA ABOUT THAT PARTICULAR SIDE OF YOU.
 WRITE IN A 3 IF YOU KNOW YOU HAVE TALKED FULLY TO ANOTHER PERSON ABOUT THAT ITEM. USE A 2 ONLY FOR THOSE TOPICS WHERE YOU KNOW ANOTHER PERSON HAS FULL AND ACCURATE INFORMATION ABOUT YOU BECAUSE YOU HAVE TAKEN THE TROUBLE TO CONFIDE FULLY.

50. Characteristics of my parents that I dislike. _____
51. The things in my past or present life about which I am most ashamed. _____
53. The aspects of my body I am most satisfied or dissatisfied with. _____
54. Disappointments I have experienced with sex. _____
55. How I react to other's criticism and praise of me. What are the things they criticize and praise in me? _____
56. How often I have sexual experiences and the nature of these experiences. _____
57. The kind of person with whom I'd like to have sexual experiences _____
58. The aspects of my personality that I dislike, worry about, or regard as a handicap to me. _____
59. Feelings about my sexual adequacy. _____

Many people experience difficulty in handling interpersonal situations requiring them to assert themselves in some way, for example, turning down a request, asking a favor, giving someone a compliment, expressing disapproval or approval, etc. Please indicate your degree of discomfort or anxiety in the space provided before each situation listed below. Use the following scale:

- 1 = none
- 2 = a little
- 3 = a fair amount
- 4 = much
- 5 = very much

Then, go over the list a second time and note after each item the probability or likelihood of your doing the behavior if actually presented with the situation.* For example, if you rarely apologize when you are at fault, you would mark a "4" after that item. Use the following scale to indicate response probability.

- 1 = always do it
- 2 = usually do it
- 3 = do it about half the time
- 4 = rarely do it
- 5 = never do it

*NOTE - It is important to cover your discomfort ratings (located in front of the items) while indicating response probability. Otherwise, one rating may influence the other. To correct for this, place a piece of paper over your discomfort ratings while responding to the situations a second time for response probability.

Degree of Discomfort	Situation	Response Probability
_____	60. Turn down a request to borrow your car	_____
_____	61. Compliment a friend	_____
_____	62. Ask a favor of someone	_____
_____	63. Resist sales pressure	_____
_____	64. Apologize when you are at fault	_____
_____	65. Turn down a request for a meeting or date	_____
_____	66. Admit fear and request consideration	_____
_____	67. Tell a person you are intimately involved with when he/she says or does something that bothers you	_____
_____	68. Ask for a raise	_____
_____	69. Admit ignorance in some area	_____
_____	70. Turn down a request to borrow money	_____
_____	71. Ask personal questions	_____
_____	72. Turn off a talkative friend	_____
_____	73. Ask for constructive criticism	_____
_____	74. Initiate a conversation with a stranger	_____
_____	75. Compliment a person you are romantically involved with or are interested in	_____
_____	76. Your initial request for a meeting is turned down and you ask the person again at a later time	_____
_____	77. Admit confusion about a point under discussion and ask for clarification	_____
_____	78. Apply for a job	_____
_____	79. Ask whether you have offended someone	_____
_____	80. Tell someone that you like them	_____

81. Request expected service when such is not forthcoming, e.g., in a restaurant
82. Discuss openly with the person his/her criticism of your behavior
83. Return defective items, e.g., store or restaurant
84. Express an opinion that differs from that of the person you are talking to
85. Resist sexual overtures when you are not interested
86. Tell the person when you feel he/she has done something unfair to you
87. Accept a date
88. Tell someone good news about yourself
89. Resist pressure to drink
90. Resist a significant person's unfair demand
91. Quit a job
92. Resist pressure to "turn-on"
93. Discuss openly with the person his/her criticism of your work
94. Request the return of borrowed items
95. Receive compliments
96. Continue to converse with someone who disagrees with you
97. Tell a friend or someone with whom you work when he/she says or does something that bothers you
98. Ask a person who is annoying you in a public situation to stop

This inventory consists of a number of statements describing your feelings and reactions toward your lover, someone you've been in a relationship with for six months or more. If you are not presently involved in such a relationship, answer the statements with respect to your past lover. If you have never had a long-term lover, answer the statements with respect to your ideal lover, someone you can see yourself having a relationship with. Answer each item "true" or "false" for one type of lover. Circle which type of lover you are responding for:

	CURRENT	PAST	IDEAL		True	False
99.	I like to take care of him when he is sick					
100.	I respect his individuality					
101.	I can understand the way he feels					
102.	I want to know details about things he does					
103.	I feel guilty when I am selfish with him					
104.	I am afraid of making mistakes around him					
105.	I like him just as he is, with no changes					
106.	I have a need to be needed by him					
107.	I make many demands on him					
108.	I feel very possessive toward him					
109.	I have the feeling that we are "buddies" together					
110.	I share important common interests with him					

- | | TRUE | FALSE |
|--|-------|-------|
| 111. I care for him even when he does things that upset or annoy me | _____ | _____ |
| 112. I am bothered by fears of being stupid or inadequate with him . | _____ | _____ |
| 113. I have a feeling for what his experiences feel like to him. . . | _____ | _____ |
| 114. I really value him as an individual or a unique person | _____ | _____ |
| 115. I seek a great deal of privacy with him | _____ | _____ |
| 116. I feel it necessary to defend my past actions to him | _____ | _____ |
| 117. I like to tease him | _____ | _____ |
| 118. Criticism from him makes me doubt my feelings about my own worth | _____ | _____ |
| 119. I feel deeply his most painful feelings | _____ | _____ |
| 120. My relationship with him is comfortable and undemanding | _____ | _____ |
| 121. My feeling for him is often purely physical . | _____ | _____ |
| 122. I have tastes in common with him which others do not share. . . | _____ | _____ |
| 123. I spend a lot of time thinking about him | _____ | _____ |
| 124. I know the weaknesses I see in him are also my weaknesses . . . | _____ | _____ |
| 125. I like to express my caring by kissing him on the cheek | _____ | _____ |
| 126. I feel free to show my weaknesses in front of him | _____ | _____ |
| 127. My feeling for him has a rough, strong, even fierce quality . . | _____ | _____ |
| 128. I know him well enough that I don't have to ask for the details of his activities | _____ | _____ |
| 129. It is easy to turn a blind eye to his faults | _____ | _____ |
| 130. I try to understand him from his point of view | _____ | _____ |
| 131. I want what is best for him | _____ | _____ |
| 132. I can care for myself in spite of his feelings for me | _____ | _____ |
| 133. I am afraid to be myself with him | _____ | _____ |
| 134. My good feelings for him come back easily after quarrels | _____ | _____ |
| 135. My feeling for him is independent of other relationships. . . | _____ | _____ |
| 136. I care for him enough to let him go, or even to give him up . | _____ | _____ |
| 137. I like to touch him | _____ | _____ |
| 138. My feeling for him is based on his accomplishments | _____ | _____ |
| 139. My feeling for him is an expression of what I might call my love for Mankind | _____ | _____ |
| 140. The expression of my own needs is more important than pleasing him | _____ | _____ |
| 141. My caring for him is characterized by a desire to promise to commit my life completely to him | _____ | _____ |
| 142. I require appreciation from him | _____ | _____ |
| 143. I care for him even when he is stupid | _____ | _____ |
| 144. My relationship to him has a quality of exclusiveness or "we-ness" | _____ | _____ |
| 145. My caring for him means even more than my caring for myself . | _____ | _____ |

- | | | |
|---|-------|-------|
| 146. He seems to bring out the best in me | _____ | _____ |
| 147. I feel that I have to give him reasons for my feelings . . . | _____ | _____ |
| 148. Being rejected by him changes my feelings for him | _____ | _____ |
| 149. I would give up almost anything for him | _____ | _____ |
| 150. I feel I can say anything I feel to him | _____ | _____ |
| 151. My feeling for him has a quality of forgiveness | _____ | _____ |
| 152. I can be aggressive and positive with him | _____ | _____ |
| 153. I feel that we "stand together" against the views of
outsiders | _____ | _____ |
| 154. I feel a strong sense of responsibility for him | _____ | _____ |
| 155. I live with him in terms of my wants, dislikes, and values . | _____ | _____ |
| 156. Sometimes I demand that he meets my needs | _____ | _____ |
| 157. My feeling for him has a strong jealous quality | _____ | _____ |
| 158. My feeling for him has a quality of patience | _____ | _____ |
| 159. I can tell what he is feeling even when he doesn't talk
about it | _____ | _____ |
| 160. I appreciate him | _____ | _____ |
| 161. I feel he is a good friend | _____ | _____ |
| 162. I have a need to give or do things for him | _____ | _____ |
| 163. My feeling for him has a quality of compassion or sympathy . | _____ | _____ |
| 164. I have a strong physical desire for him | _____ | _____ |
| 165. I can be inconsistent or illogical with him | _____ | _____ |
| 166. I have a strong need to be near him | _____ | _____ |
| 167. I can be both strong and weak with him | _____ | _____ |
| 168. It seems as if I have always felt caring for him from the
first moment I knew him | _____ | _____ |
| 169. I am afraid to show my fears to him | _____ | _____ |
| 170. I have a deep feeling of concern for his welfare as a human
being | _____ | _____ |
| 171. My relationship to him is characterized by a deep feeling of
camaraderie or comradeship | _____ | _____ |
| 172. I have a feeling of appreciation of his value as a human
being | _____ | _____ |
| 173. My giving toward him is characterized by overflow, not
sacrifice | _____ | _____ |
| 174. My caring for him sometimes seems to be exclusively physical . | _____ | _____ |
| 175. I am afraid to show my tears in front of him | _____ | _____ |
| 176. I like to express my caring for him by caressing him a
great deal | _____ | _____ |

TRUE FALSE

177. His caring for me exerts a kind of restrictive power over me . _____
178. My relationship with him is characterized by trust _____
179. I have a need to control his relationships with others _____
180. I am able to expose my weaknesses easily to him _____
181. I feel he has infinite worth and dignity _____



A sore below the knee

Wilfred E. Wooldridge, M.D.
Springfield, Mo.

A 60-year-old housewife complained of a crusty sore a little below the right knee. From her description, the lesion began as a small, round raised pustule, had grown slowly for 4 months, and was surprisingly asymptomatic. Otherwise, her health was good.



What would be your diagnosis? We considered these.

- | | |
|--|--|
| ☐ Halide dermatitis | ☐ Tertiary syphilis |
| ☐ Sporotrichosis | ☐ Blastomycosis |
| ☐ Stasis ulcer | |

Answer

Halide dermatitis seemed like a good possibility because ingestion of bromides or iodides can cause unexpected shin lesions that develop slowly; but these lesions are usually multiple. Since our patient had only one lesion, and since a careful history showed she had not been taking halides, we ruled out halide dermatitis.

Sporotrichosis was a reasonably good possibility because it can appear as a single lesion. However, the characteristic ascending subcutaneous nodules were absent, so we dismissed this diagnosis.

Stasis ulcer was considered, only to be quickly eliminated. For one thing, the front of the knee would be an unusual location. And there would be obvious

evidence of varicose veins, edema, and hemosiderin pigmentation—which this woman did not have. Also, the lesion would probably be bilateral, unless the involved leg had been injured by an old thrombophlebitis, which the woman denied.

A diagnosis of tertiary syphilis was not so easy to exclude, even though those lesions now occur only rarely. Like this woman's sore, a tertiary syphilis lesion can be solitary and asymptomatic, but it would probably evolve more slowly.

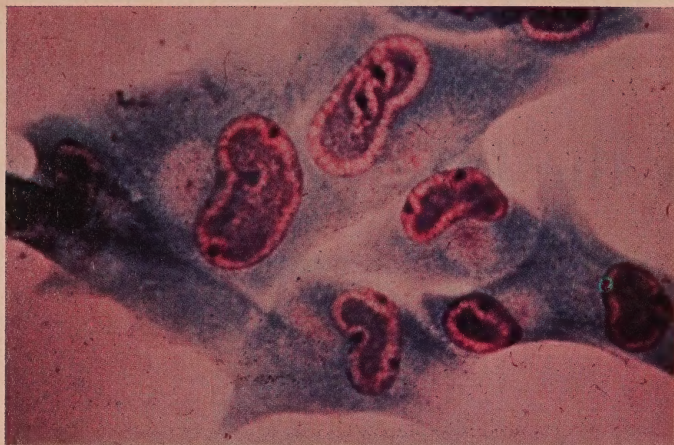
Blastomycosis was the correct diagnosis, but one that would have been easy to overlook because of its rarity. This woman's infection was atypical, since she had no accompanying lung infection or other signs of systemic

involvement. Still, the blastomycotic lesion is distinctive, and its organism identifiable by a few simple procedures.

Potassium hydroxide mounts from the peripheral pustules yield thick-walled, rounded, refractile, spherical, and sometimes budding cells. Culture of these pustules should be positive on dextrose-Sabouraud's agar at room temperature. Subculture on blood agar at 37° C may yield the organism in its yeast phase. Furthermore, the periodic acid-Schiff (PAS) stain of a biopsy taken from the periphery of the lesion should also reveal the organism.

We treated the infection with intravenous amphotericin B, with a good response and no recurrence.





Figure—Human fibroblasts in a culture infected with cytomegalovirus showing intranuclear inclusions; Giemsa's stain.

titles of virus. The distinction is not absolute, however.

Other tests

Cytologic examination of the urine sediment is not a good diagnostic test. Very few cytologists have the experience to be sure of the findings, and only a

"The outstanding fact about the epidemiology of cytomegalovirus is that 1% of all infants born in the U.S. have been infected in the uterus."

third of infected newborns have typical inclusion-bearing cells in their urine (Figure). Also, the likelihood of finding inclusion cells in the urine decreases later in infancy, even though the patient may continue to excrete the virus in his urine.

Serologic testing of the newborn and of the mother can be helpful. A newborn who has a high titer of complement-fixing antibodies against CMV can be suspected of having congenital cytomegalovirus infection. Per-

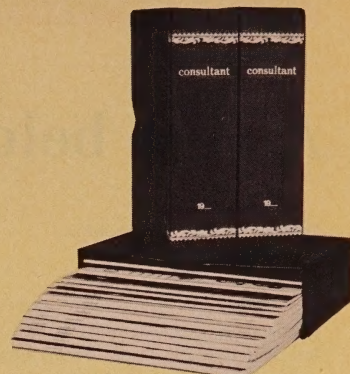
sistence of the high titer after the child should have lost his passive antibodies confirms the serologic diagnosis. The demonstration of CMV-specific IgM antibodies in the infant's serum by indirect hemagglutination or indirect immunofluorescence is also diagnostic. However, the IgM level is often normal in mild CMV infections.

Management

On recognizing a CMV infection, counsel the parents about the cause of the child's problem and follow the patient closely. Specific treatment is not available. Cytosine arabinoside and adenine arabinoside have a temporary suppressive effect on virus excretion, but no proven effect in lessening the patient's brain damage. Transfer factor is being investigated as a possible treatment for cytomegalovirus.

Perhaps immunization against the virus will be the best form of treatment. Prophylactic vaccination against CMV with attenuated viruses is being studied in my laboratory and at St. George's Hospital in London.

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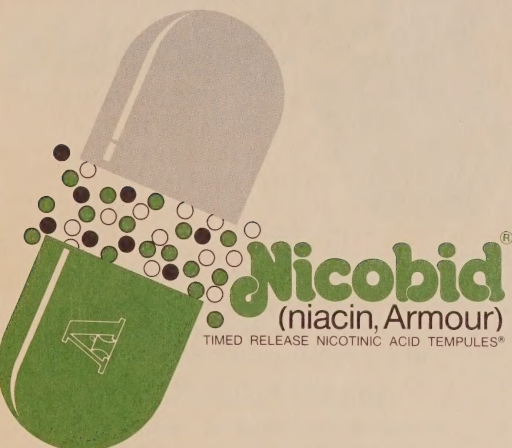
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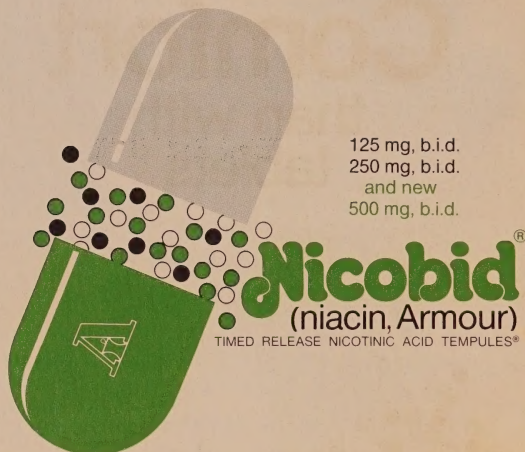
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develop viremia, and in a pregnant woman the virus may cross the placenta and infect the fetus. The mother excretes virus from her throat and urine for many months, and subsequent to its birth, so will her infant. Indeed, the infant may continue to excrete the virus for several years.

The other cycle is a venereal one. Evidence for it comes from the fact that up to 15% of women excrete cytomegalovirus from the cervix, and the virus occurs in the semen of at least 3% of men. The first cycle might lead to the second, as when a man with viremia develops a CMV infection in the genital tract and begins to secrete the virus in his semen, but there is no proof of this at the moment. The significance of the venereal cycle to intrauterine infection is uncertain, but it is clear that presence of the virus in the cervix can cause a perinatal infection when the infant passes through the vagina.

Symptoms: usually mild

A disease as common as neonatal CMV infection should be easily diagnosed. One reason that it isn't is that the symptoms are usually mild. A newborn's brain damage and hearing loss may not become apparent until much

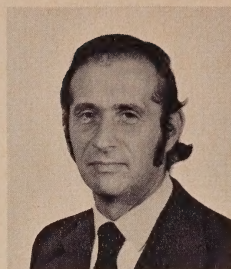
later in childhood. Diagnosis is usually made only in the full-blown syndrome when the infant has microcephaly, hepatosplenomegaly, thrombocytopenia, and evidence of intrauterine growth retardation. A list of clinical findings is given in the Table. However, one or more of the following signs in an infant is most helpful in making the diagnosis:

- Small size for gestational age
- Microcephaly
- Thrombocytopenia
- Prolonged jaundice, especially if the conjugated bilirubin is elevated
- Chronic interstitial pneumonia
- Chorioretinitis.

Perinatal infection occurs with great frequency, but most infants remain asymptomatic. Some infants show chronic interstitial pneumonia because of acquiring the CMV infection at the time of birth or shortly thereafter.

Diagnosis: viral isolation

The key point about diagnosis of CMV is that it must be made by isolating the virus. All other methods are less helpful. The best source for the virus is the patient's urine. Ideally, urine should be collected by suprapubic puncture to minimize bacterial contamination. A "clean-catch" urine can be treated by



Dr. Plotkin is professor of pediatrics at the University of Pennsylvania School of Medicine and professor at the Wistar Institute of Anatomy and Biology. He has been certified by the American Board of Pediatrics and is a member of the American Association of Immunologists, the American Pediatric Society, and the Infectious Disease Society of America.

the virologist with antibiotics, but unless the virus laboratory receives the specimen promptly, bacterial growth may interfere with viral culture.

Cytomegalovirus is a labile virus, but its lability can be overemphasized. If urine is kept at 0° to 4°C (not frozen), the cytomegalovirus in it remains viable for a long time. Therefore, it is possible to send a urine specimen to a distant laboratory if it is packed in ice cubes or the chemical ice cans used for picnic hampers. CMV may be identified in tissue culture of urine specimens in only 2 days if it is present in high titer, but if present in low titer, isolation may take much longer.

Finding CMV in an infant's urine does not indicate whether the infection was intrauterine or whether it occurred at the time of birth or shortly thereafter. However, the amount of virus present helps indicate the type of infection. A congenitally infected infant secretes 10⁵ or more infectious virus particles per ml of urine during the first few months of life, whereas infants infected later often excrete smaller quan-

Clinical findings in CMV infections

Central nervous system:	Microcephaly, calcifications, brain damage
Eyes:	Chorioretinitis, optic atrophy
Ears:	Deafness
Palate:	High arch
Lungs:	Pneumonitis
Heart:	Anatomic defects
Liver:	Hepatitis
Spleen:	Splenitis
Bones:	Dislocation of hip, metaphyseal lesions
Muscles:	Diastasis recti abdominis, inguinal hernia
Blood:	Thrombocytopenia, hemolytic anemia

The 'invisible' epidemic: cytomegalovirus

Stanley A. Plotkin, M.D.

If you were told that an infection that damages 1 in 700 children is largely unknown to the layman, and even to many physicians, you would probably be astonished. Yet it appears that cytomegalovirus, or CMV, is responsible for an "invisible" epidemic of birth defects. In fact, cytomegalovirus is as common a cause of congenital defects as Down's syndrome.

The epidemic isn't really invisible, of course. Cytomegalovirus causes distinct clinical findings, though much remains to be learned about this herpes-group virus. We do know that it has a DNA-containing core, a lipid envelope, and that it is morphologically indistinguishable from *herpes simplex*. Like other herpesviruses, it has the property of latency; after the primary infection it can persist in the patient and be reactivated later in life.

The outstanding fact about the epidemiology of cytomegalovirus is that 1% of all infants born in the U.S. have been infected in the uterus. Estimates of the morbidity of this group of infants varies, but at least 15% suffer

brain damage and another 15% to 20% may suffer hearing loss. Thus the infection damages about 1 in 700 newborns, and perhaps as many as 1 in every 300.

It appears that up to 3% of pregnancies are complicated by a cytomegalovirus infection. Unfortunately, most adult infections are asymptomatic or not serious enough to call for a visit to the physician, which explains the general lack of awareness of the disease. Two syndromes in the adult should alert you to the possibility of cytomegalovirus infection. The first is hepatitis without laboratory evidence of hepatitis B or epidemiologic suggestion of hepatitis A. The second is infectious mononucleosis with a *negative* heterophil antibody test.

Transmission method

We don't yet know the method of transmission of CMV, but it is thought that the infection is passed in two ways. One cycle is probably mediated through virus-containing saliva or other respiratory secretions. A seronegative person who comes in contact with the secretions is infected. The infected person may

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Physical diagnosis of rheumatic disease

Rodney Bluestone, M.B., M.R.C.P.

Diagnosis of most types of typical chronic rheumatic disease depends largely on an accurate assessment of the areas of involvement, using clinical and radiographic examination. The presence or absence of certain extra-articular features provides supportive clues. Only in atypical or very acute disease is laboratory diagnosis mandatory.

The most common arthropathies are:

- Degenerative joint disease or osteoarthritis, a wear-and-tear process affecting older people, with only a very occasional inflammatory component.
- Soft-tissue rheumatism syndromes such as shoulder-joint capsulitis and tennis elbow, in which musculoskeletal pain and dysfunction appear to arise locally with no evidence of systemic or chronic inflammatory disease.
- Chronic inflammatory arthropathies such as rheumatoid arthritis, predominantly affecting young to middle-aged women; and rheumatoid variants such as

ankylosing spondylitis, Reiter's syndrome, and psoriatic arthritis, predominantly affecting young men.

- Synovitis, such as crystal-induced synovitis (sodium urate gout), almost exclusively affecting middle-aged and elderly men; and calcium pyrophosphate synovitis (pseudogout), a disease of the elderly with no sex preference.
- Acute septic arthritis, frequently caused by gonococcal septicemia in sexually active young adults.
- Some collagen-vascular diseases such as systemic lupus erythematosus, with conspicuous arthropathy that resembles other chronic rheumatic disorders.

Physical signs

The cardinal sign of true arthritis is joint swelling. Although joint pains are a very common symptom, they often do not indicate rheumatic disease. You cannot, therefore, be certain of an inflammatory arthritis unless you find visible or palpable synovial distention. Occasionally, however, painful limitation of

joint motion without a readily detectable synovial effusion indicates past or recent synovitis. Moreover, the typical joint affected by osteoarthritis may be painful to move and may appear hypertrophied (due to bony marginal osteophytes), but only rarely has an obvious effusion.

The clinical profiles

Osteoarthritis. This disease has a peculiar tendency to affect particular joints, including the distal interphalangeal and thumb joints of the hands; the lower cervical and lumbosacral spine; the hips and knees; and the big toe joints often associated with hallux valgus deformities. In addition, the temporomandibular joints tend to develop osteoarthritis at a much earlier age than do the other joints. Pain, mild tenderness, and painful limitation of motion with crepitus are the principal findings. X-ray studies tend to confirm this pattern of involvement even in asymptomatic areas. They reveal the characteristic irregular loss of joint space, subchondral bony sclerosis, and marginal osteophyte formation. Osteo-

WHEN "GRAY AREA" SYMPTOMS START TO AFFECT THE ELDERLY PATIENT'S LIFE

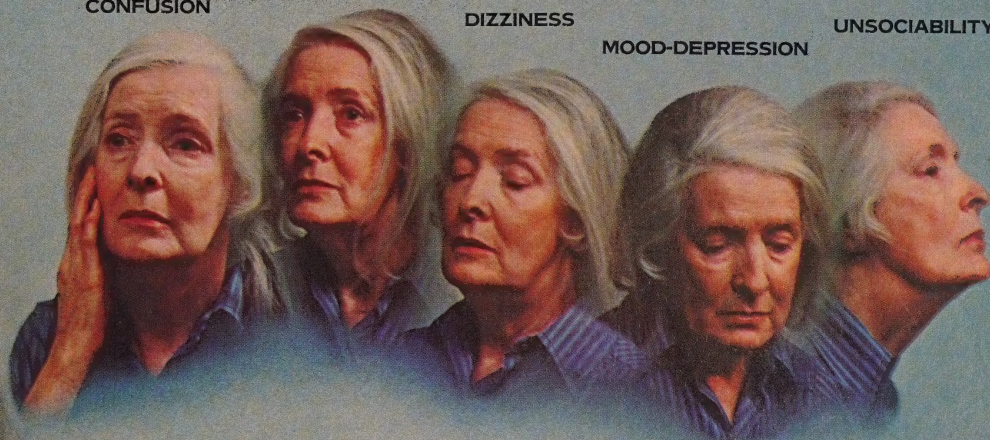
CONFUSION

LACK OF SELF-CARE

DIZZINESS

MOOD-DEPRESSION

UNSOCIABILITY



The elderly patient with "gray area" symptoms may not always be aware of these early and subtle changes...or able to articulate them. But the patient may be humiliated and hurt by the inability to control confusion, lack of self-care, dizziness, mood-depression, and unsociability...problems that can alienate patient from family, from friends, and even from self.

Hydergine therapy can often bring these patients meaningful help. Given early—when symptoms are still mild to moderate—Hydergine therapy may retard or improve "gray area" symptoms.

TO HELP RELIEVE
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GIVE ENOUGH, SOON ENOUGH,
LONG ENOUGH

For Brief Summary, please see following page.



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- Helps assure optimal dosage because of better adherence to dosage regimen.
- Oval shape of 1-mg tablet makes it easier for the elderly patient to identify.

Contraindications: Hypersensitivity to the drug.

Precautions: *Because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing Hydergine sublingual tablets.*

Adverse Reactions: Serious side effects have not been found. Some sublingual irritation, transient nausea, and gastric disturbances have been reported. Hydergine sublingual tablets do not possess the vasoconstrictor properties of natural ergot alkaloids.

Dosage and Administration: 1 mg sublingually three times daily. Alleviation of symptoms is usually gradual and results may not be observed for 3-4 weeks.

WHEN "GRAY AREA" SYMPTOMS START TO AFFECT THE ELDERLY PATIENT'S LIFE

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Each 1-mg Hydergine sublingual tablet contains dihydroergocornine 0.333 mg, dihydroergocristine 0.333 mg, and dihydroergokryptine 0.333 mg. (Dihydro- α -ergokryptine and Dihydro- β -ergokryptine in the proportion of 2:1) as the mesylates, representing a total of 1.0 mg

or other amphetamines. Attempts to diagnose depression in these patients are complicated by the extremely high incidence of gastrointestinal complaints.

In a random sample of the general population—1,645 adults ages 17 to 92—we found that 5% to 7% complained of indigestion, constipation, or nervous stomach “regularly”; 18% to 20% complained “occasionally.” Twenty-nine percent reported weight difficulties, while complaints of stomachache and diarrhea were less common. It is no wonder that physicians almost daily find it necessary to differentiate depression and GI dysfunction.

Five major combinations of depression and gastrointestinal dysfunction stand out:

- Depression simulating GI dysfunction
- Depression preceding serious GI dysfunction
- Concurrent depression and GI dysfunction
- Depression following GI dysfunction
- Depression as a reaction to grief.

When depression simulates GI dysfunction

Depression simulating gastrointestinal dysfunction is probably the most frequent combination of the two disorders. Patients may complain of symptoms in any part of the GI tract, from mouth to anus: dryness of the mouth, loss of appetite, overeating, indigestion, abdominal pain, diarrhea, or constipation. They may tell you of family or other personal problems, unsatisfactory working situations, or the loss of a loved one through illness, separation, or death. After a thorough history and workup, the physician may (particularly if no structural lesion is occurring) label the patient “func-

tional.” Too often a diagnosis of functional GI disorder precludes definitive antidepressant therapies. But many of these patients are depressed and should be treated for depressive illness.

When depression precedes serious GI illness

For many patients, particularly in their 50s and 60s, with no previous history of depressive illness, the first signs of cancer of the pancreas or a retroperitoneal lymphoma is depression: crying spells, insomnia, anxiety, and premonitions of serious illness. Often these patients are referred for psychotherapy, and after a few months, when the malignancy becomes apparent, the psychiatrist, the gastroenterologist, and the surgeon are all dismayed.

A few years ago at the Mayo Clinic, Fras, Litin, and Pearson* studied 139 preoperative patients suspected of having either cancer of the pancreas or cancer of the colon. These two groups were used because, before surgery, depressive symptoms had occurred in about 20% of the patients with cancer of the pancreas, but occurred very infrequently in patients with cancer of the colon. After surgery, 46 were found to have cancer of the pancreas, 64 had cancer of the colon, and 29 had other GI disorders. Of the patients with cancer of the pancreas, 50% had reported depressive mental symptoms on an average of 6 months before their first indication of illness. A total of 76% reported mental symptoms sometime before surgery—in contrast to 20% with other GI illnesses who reported mental symptoms.

We can only speculate about

* Fras, L., Litin, E.M., and Pearson, J.S.: Comparison of psychiatric symptoms in carcinoma of the pancreas with those in some other intra-abdominal neoplasms. *Am. J. Psychiatry*, 123 (12): 1553-1562, 1976.

the mechanism of depression in patients with cancer of the pancreas. It is possible that the malignancy, even in its very early stages, produces autonomic or hormonal dysfunction that may in turn produce depression. Another possibility is that the malignancy interferes with the absorption and metabolism of the precursors of the catecholamines.

When depression and GI dysfunction are concurrent

In an inpatient study, we evaluated the occurrence of depression and structural GI disease together. We tried to determine which symptoms (other than those related to GI function) to look for to diagnose a simultaneous depression among patients with structural GI disease. These five symptoms differentiated the depressed patients with GI disease and the nondepressed: headache, chest pain, diminished interest in sexual activity, guilt, and self-hate. We concluded that to diagnose depression in patients with gastrointestinal disorders, physicians must be alert to syndromes in which loss of self-esteem (a reflection of guilt and self-hate) is combined with prolonged physical complaints. The five distinguishing symptoms present a pervasive, distressing syndrome. When two of these, chronic headache and chest pain, are coupled with GI distress, all the body is involved except the extremities. Add marked loss of sexual interest, and the genitourinary system is also affected.

When depression follows GI dysfunction

Depression following in the wake of gastrointestinal disorder (or any major illness) is a common sequence and a much-

The Septra[®] Ba

Each tablet contains:

80 mg trimethoprim and 400 mg sulfamethoxazole

A strong in vitro record¹

E coli

Septra 95%
of 220517 isolates

Cephalosporin 79%

of 358025 isolates

Ampicillin 74%

of 351311 isolates

Nitrofurantoin 95%

of 338756 isolates

Proteus sp

Septra 91%
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Cephalosporin 81%*

of 106281 isolates

Ampicillin 77%*

of 104437 isolates

Nitrofurantoin 13%

of 100829 isolates

*Indicated in approved drug information
for *Proteus mirabilis* only.

Enterobacter

Septra 87%
of 9896 isolates

Cephalosporin 32%†

of 14986 isolates

Ampicillin 15%†

of 14036 isolates

Nitrofurantoin 66%

of 14219 isolates

†Not indicated in approved drug information.

Klebsiella

pneumoniae

Septra 87%
of 46279 isolates

Cephalosporin 85%

of 76898 isolates

Ampicillin 5%†

of 76026 isolates

Nitrofurantoin 68%

of 72030 isolates

†Not indicated in approved drug information.

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lance of Power

A consistent in vivo response

Septra outperformed cephalixin

In a study of 148 patients with recurrent urinary tract infections,² bacteriologic response rate on day 14 of therapy^{††} was 99% with Septra, compared to 94% with cephalixin.[‡] This superiority of response to Septra occurred in spite of a built-in "handicap": Infecting organisms had to be susceptible *in vitro* to cephalixin, but not necessarily to Septra. Drug regimens consisted of either two Septra tablets b.i.d. or one 250 mg cephalixin pulvule q.i.d.

^{††}Results derived from urine cultures done at the midpoint of a 28-day study, since recommended duration of Septra therapy is 14 days.

[‡]Criterion for infection: 100,000 or more organisms/ml urine; criterion for clear culture: 1000 or fewer organisms/ml urine.

Septra outperformed ampicillin

In a study of 10-day therapy in 156 patients with recurrent urinary tract infections,² clear culture was maintained four days after therapy ended in 81% of patients treated with Septra, compared to 76% of those treated with ampicillin.[‡] These results gain added significance considering that causative organisms not susceptible *in vitro* to ampicillin were excluded, but no such advantage was afforded Septra. Drug regimens consisted of either two Septra tablets b.i.d. or one 500 mg ampicillin capsule q.i.d.

[‡]Criterion for infection: 100,000 or more organisms/ml urine; criterion for clear culture: 1000 or fewer organisms/ml urine.

Septra outperformed nitrofurantoin (macrocrystals)

In a study of 289 patients treated for 14 days for recurrent urinary tract infections,² bacteriologic response (measured eight days after therapy ended) to Septra was 94%, compared to 90% with nitrofurantoin.[‡] Drug regimens consisted of either two Septra tablets b.i.d. or one 100 mg capsule of nitrofurantoin macrocrystals q.i.d.

[‡]Criterion for infection: 100,000 or more organisms/ml urine; criterion for clear culture: 1000 or fewer organisms/ml urine.

In vitro antibacterial action well balanced by clinical success

Septra® DS

Each tablet contains:

160 mg trimethoprim and 800 mg sulfamethoxazole
in recurrent urinary tract infections
due to susceptible organisms[#]

[#]It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Artist's conception of major uropathogens.

See next page for prescribing information.

In recurrent urinary tract infections due to susceptible organisms*

Septra® DS Tablets

Each tablet contains:

**160 mg trimethoprim and
800 mg sulfamethoxazole**

Septra® Suspension

Each teaspoonful (5 ml) contains:

**40 mg trimethoprim and
200 mg sulfamethoxazole**

In vitro antibacterial action well balanced by clinical success

- convenient b.i.d. dosage schedule helps insure patient compliance
- pleasantly flavored cherry suspension available for children
- Septra and Septra DS now available in new *small-size* tablets

Rx guidelines

- during therapy, maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination
- contraindicated in children under two months old
- see prescribing information for complete guidelines

*It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

Septra®

Tablets and Suspension

Indications and Usage: Urinary Tract Infections: Urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris*, *Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination.

NOTE: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in these urinary tract infections.

The recommended quantitative disc susceptibility method (*Federal Register* 37: 20527-29, 1972) may be used to estimate bacterial susceptibility to Septra. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Septra therapy. "Intermediate susceptibility" also indicates that response is likely and "Resistant" that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides. Pregnancy and during the nursing period. Infants less than two months of age.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias. Experience with trimethoprim alone is much more limited, but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides.

Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBCs are recommended; therapy should be discontinued if a significant reduction in the count of any formed blood element is noted.

Precautions: Use with caution in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In glucose-6-phosphate dehydrogenase-deficient individuals, hemolysis may occur (frequently dose-related). During therapy maintain adequate fluid intake and perform frequent urinalyses with careful microscopic examination and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Septra. **Blood Dyscrasias:** Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. **Allergic Reactions:** Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. **Gastrointestinal Reactions:** Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. **C.N.S. Reactions:** Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. **Miscellaneous Reactions:** Drug fever, chills, and toxic nephrosis with oliguria and anuria. Perianteritis nodosa and L. E. phenomenon have occurred. Due to certain chemical similarities to some

goitrogens, diuretics (acetazolamide and the thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia; cross-sensitivity may exist with these agents. In rats, long-term administration of sulfonamides has produced thyroid malignancies.

Dosage and Administration: Not recommended for use in infants less than two months of age.

Adults: The usual adult dosage for the treatment of urinary tract infections is one double strength tablet or two regular tablets or four teaspoonfuls (20 ml) every 12 hours for 10 to 14 days. Shake suspension well before using.

Children: Recommended dose is 8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, given in two divided doses for 10 days. The following table is a guideline for the attainment of this dosage using Septra Tablets or Suspension.

Children: Two months of age or older

lb	kg	Dose — every 12 hours	
		Teaspoonfuls	Tablets
20	9	1 (5 ml)	½
40	18	2 (10 ml)	1
60	27	3 (15 ml)	1½
80	36	4 (20 ml)	2 (or 1 DS tablet)

For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual Standard Regimen
15-30	Half of the Usual Dosage Regimen
Below 15	Use Not Recommended

Supplied: Septra DS (Double Strength) tablets containing 160 mg trimethoprim and 800 mg sulfamethoxazole — bottles of 60 tablets and unit dose packs of 100. Septra tablets containing 80 mg trimethoprim and 400 mg sulfamethoxazole — bottles of 40, 100, 500, and 1000 tablets and strip packages of 100 individually packed tablets. Oral suspension, containing the equivalent of 40 mg trimethoprim and 200 mg sulfamethoxazole in each teaspoonful (5 ml), cherry flavored — bottles of 450 ml.

References: 1. PMR Bacteriology Report — urine cultures only. National summary Dec 1975. Jan 1976. Feb 1976. (From 200 acute care hospitals of 100 beds or more.) Data on file, Burroughs Wellcome Co.

2. Data on file, Burroughs Wellcome Co.



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neglected area of practice. Prolonged illness or convalescence affects the sick person's self-image as well as his relationships—familial, medical, and societal. He is anxious about his vulnerability, yet longs for attention and service.

Often the patient convalescing from a gastrointestinal disorder has difficulty with digestion and elimination and may require a special diet. These problems can awaken childhood conflicts and fantasies about feeding and bowel training, further stimulating a sense of helplessness. In addition, the patient may be faced with realistic fears of pain, disability, and financial limitations. This continual struggle for adaption can easily result in lowered self-esteem and depression.

Reactions to a bout of hepatitis, for example, are well known. The so-called "normal" posthepatic syndrome consists of lethargy, self-concern, lowered mood, loss of motivation, and loss of appetite. Irritability is common. We now question whether, in fact, the posthepatic syndrome is actually distinguishable from real depression; moreover, antidepressant therapy probably should be used more often with these patients than it is.

When grief mimics GI dysfunction

The following case history is an example of grief turned inward. During a 2-year period, a 30-year-old minister's wife had numerous gastrointestinal evaluations for right upper quadrant pain; the only abnormal findings were obesity and "sluggish emptying of the gallbladder." But then, a few hours before she was to leave the hospital, her gastroenterologist found her crying

alone in her room and referred her for psychiatric consultation.

At first, she insisted that she did not need psychiatric attention. But we began taking a careful personal history and soon discovered that her mother had died suddenly 2 years before. During the funeral, her husband—one of the small town's most prominent ministers—told her that she must not break down. He felt that his work required that they comfort the bereaved, and that any sign of excessive grief on her part would be interpreted as weakness, harming his career and diminishing their position in the community.

She told us that she faithfully followed his instructions, functioning stoically during the following months. Poignantly, she admitted crying for a few moments when she was alone. Fortunately, we saw this woman at an opportune time. Understanding her distress and encouraging her to grieve about her loss produced excellent results in only five visits. In fact, 1 month after we originally saw her, she was cheerful and happy and had voluntarily placed herself on a sensible diet. Not surprisingly, her pain had practically disappeared.

The depressive syndrome

To diagnose depressive illness, look for at least three or four of these five major symptoms:

- Sadness
- Feelings of self-hate, guilt, suicidal tendencies, and lowered self-esteem
- A dismal outlook on the future, or despair about the meaning of life
- A disturbance in sleep, eating, elimination, or sexual drive
- Physical disorders, including genitourinary, cardiorespiratory,

and especially gastrointestinal complaints and dysfunctions.

Some physical symptoms should be present for a positive diagnosis. Remember that loss of appetite and constipation are not necessarily the typical gastrointestinal manifestations of depressive illness. Also, sleep problems may appear as unrefreshing or intermittent sleep or too much sleep, and the disturbance in sexual drive may appear as relatively unsatisfying hypersexuality, particularly during the early weeks or months of depression.

A comprehensive treatment program is well within the scope of the family physician. Most such depressed patients do not require psychiatric referral, although a "one-shot" consultation may help confirm the diagnosis and assist with the treatment. A comprehensive treatment regimen combines psychotherapy, medication, and resocialization.

Psychotherapy

Talk with and listen to the patient. Explore the meaning and depth of his loss or sense of loss. It may be tangible or easily understood, or it may be symbolic, threatening, or imaginary.

Encourage the patient to express his feelings. Many patients are reluctant to reveal ambivalent emotions (for example, guilt and grief after a death) for fear of censure or of being considered a weakling.

Learn what factors have led to lowered self-esteem—and why. Since this is the critical factor in depression, bringing it to light often provides the patient with enough insight to function more effectively and to face life with renewed courage and optimism.

Clarify any practical factors that may need to be aired and resolved for the patient to feel



Arlidin[®] 6 mg. (nylidrin HCl) **Vasodilator/Vasorelaxant**

**Where there is a
vasospastic component
to vascular disease***

Helps increase blood supply

Acts directly at the arteriolar wall to relieve vasospasm associated with sclerotic disorders*

Maintains mean arterial blood pressure

No postural hypotension reported in over a decade of use†

Encourages patient activity

Symptomatic improvement through relief of vasospasm may enhance ability to function

Usual dosage: 6 mg. t.i.d. for at least 4 weeks titrating to 12 mg. t.i.d. or q.i.d. if necessary

†See Adverse Reactions section in Brief Summary

Brief Summary

*Indications: Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified this drug as "possibly" effective for peripheral vascular disease and circulatory disturbances of the inner ear. Final classification of the less-than-effective indications requires further investigation.

Contraindications: Acute myocardial infarction, paroxysmal tachycardia, progressive angina pectoris and thyrotoxicosis. **Warnings:** In patients with cardiac disease such as tachyarrhythmias and uncompensated congestive heart failure, the benefit/risk ratio should be weighed prior to therapy and reconsidered at intervals during treatment. **Adverse Reactions:** Trembling, nervousness, weakness, dizziness (not associated with labyrinthine artery insufficiency), palpitations, nausea and vomiting may occur. Postural hypotension, while not reported, may also occur. **Dosage:** Orally, 3 to 12 mg. three or four times a day. **How Supplied:** White, scored tablets, 6 mg. and 12 mg. Bottles of 100 and 1000; single-dose blister packs, boxes of 100 (10 x 10 strips).

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better (for example, the care of an aged and infirm parent).

Finally, get the aid of other professionals if necessary, such as clergy, nurses, social workers, and physical therapists.

Medication—long enough

Proper medication is the second major ingredient of comprehensive treatment. Amitriptyline or imipramine are effective antidepressants, but physicians often do not prescribe large enough dosages, long enough. Instead of adjusting the dosage, they tend to switch the patient to another medication. Since the side effects of these medications usually are not serious, and since the largest dosages can be given at bedtime, physicians should continue an adequate dosage for at least 1 month before switching. On occasion, we hospitalize patients who fail to respond to the tricyclic drugs. We allow a drug-free period, and then we begin using the monoamine oxidase (MAO) inhibitors while the patient is in the hospital, where we can regulate his diet and observe him carefully.

Resocialization and changes

This final third of the program should include changes in the patient's routine and, perhaps most important, the development of good social support systems. Family therapy may be necessary to resolve marital or other conflicts. Frequently, pastoral counselors, health care workers, and others not only supply encouragement and suggest activities, but also help the patient build social support systems at home and in the community, making life richer and fuller. If comprehensive treatment is vigorous and extensive, only a few depressed patients will need referral.



Thyroid function tests: what to order and when

While the new thyroid function tests can be helpful, they can also be confusing. You will want to understand what these tests measure and what can alter their results. After briefly reviewing thyroid function, Dr. Joel I. Hamburger explores a number of new tests in addition to discussing possible causes for high, normal, and low radioactive iodine uptake.

Office management of prostatitis

Acute bacterial prostatitis, chronic bacterial prostatitis, or prostatosis—which is it? The presenting symptoms are much the same: frequency, urgency, and pain in the low back or perineum. Yet the treatment is different for each. Dr. Donald J. Logan discusses ways to differentiate the three types of prostatitis and ways to treat them.

The patient who won't get well

Do any of these patients sound familiar?—the woman who obviously suffers psychic pain but insists on somatic causes; the psychotic patient with bizarre bodily symptoms; the man who has much to gain by remaining "disabled." With humor and compassion, Dr. Wilfred Dorfman tells about his experiences with difficult patients and offers suggestions on effective ways to manage and medicate them.

Relieving chronic pain without strong analgesics

Part 1 of this special feature by Dr. Mary E. Moore explores nonsteroidal anti-inflammatory agents. In addition to a comprehensive account of aspirin usage, Dr. Moore discusses phenylbutazone, indomethacin, fenoprofen, and many other analgesics. In Part 2, Dr. Moore discusses corticosteroids, psychotropics, anticonvulsants, and placebos. If you are looking for alternatives to strong narcotics, you will find these articles of practical help.

Plus much more in future issues of **consultant**

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